SHIFTING PARADIGMS IN LIVE KIDNEY DONATION AND TRANSPLANTATION

Jeff Lafranca

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SHIFTING PARADIGMS IN LIVE KIDNEY DONATION AND TRANSPLANTATION

Verschuivende gedachtepatronen betreffende nierdonatie bij leven en niertransplantatie

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Voor mijn ouders

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Chapter 1

General introduction, aim and outline of the thesis

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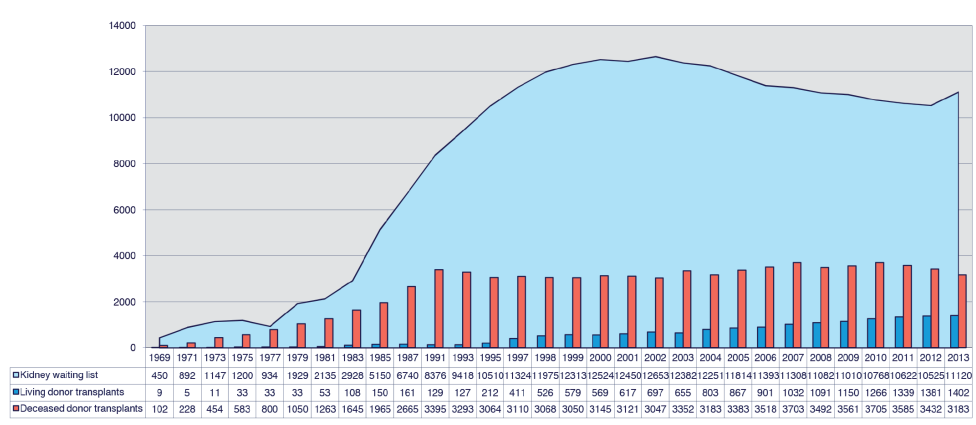
THE KIDNEY

The kidney holds several important functions; it is a filter that regulates blood pressure, maintains the acid-base balance, regulates electrolytes and produces hormones. As it produces urine, it excretes waste products like ammonium and urea. The kidney also produces erythropoietin, a glycoprotein hormone that controls erythropoiesis, or red blood cell production.

If one or more of the aforementioned functions fail, it could lead to irreversible damage, ultimately leading to end-stage renal disease (ESRD). ESRD necessitates renal replacement therapy (RRT). The three forms of RRT are haemodialysis, peritoneal dialysis and transplantation.

Although patients with ESRD can be successfully treated with haemodialysis or peritoneal dialysis, kidney transplantation is by far the best therapeutic option for the majority of patients with ESRD.[1-3] Compared with other forms of RRT, kidney transplantation leads to superior survival, improved quality of life, enhanced psychosocial development and growth in children, and a reduction of societal costs.[4,5]



	1969	1971	1973	1975	1977	1979	1981	1983	1985	1987	1991	1993	1995	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Kidney waiting list	450	892	1147	1200	934	1929	2135	2928	5150	6740	8376	9418	10510	11324	11975	12313	12524	12450	12653	12382	12225	11814	11393	11308	11082	11010	10768	10622	10525	11120
Living donor transplants	9	5	11	33	33	33	53	108	150	161	129	127	212	411	526	579	569	617	697	655	803	867	901	1032	1091	1150	1266	1339	1381	1402
Deceased donor transplants	102	228	454	583	800	1050	1263	1645	1965	2665	3395	3293	3064	3110	3068	3050	3145	3121	3047	3352	3183	3383	3518	3703	3492	3561	3705	3585	3432	3183

Data from Eurotransplant International Foundation, Annual Report 2013.

Currently, In the Eurotransplant area, on 31 Dec 2013, 11,120 patients were waitlisted for a kidney transplant; 3,183 kidneys were transplanted from a deceased donor, 1,402 from a living donor.[6]

Only 3 out of 10 patients with ESRD are transplanted; the remaining group stays on dialysis and dies while on the wait list, or is removed from the wait list because of a deteriorated clinical condition.[7] In 2013, 5,954 patients were removed from the wait list; 567 died on the list, 376 were deemed unfit for transplantation, 4,584 were transplanted, 68 recovered and 359 were removed for other reasons. An unknown factor is how many patients never make it on the wait list at all for several reasons like putative ineligibility, comorbidities, or no access to proper healthcare.

Regretfully, the shortage in donor organs prevails. Despite an impressive societal and governmental investment, the number of deceased donor kidneys that becomes available for transplantation remains insufficient to meet the demand. One of the solutions to this problem is live kidney donation. The advantages of live donor kidney transplantation are numerous and include, among others, that it is an elective operation with short ischemia times. Furthermore, in this way, transplant professionals are able to select good quality kidneys of healthy donors. Transplantation with a kidney from a living donor shows superior outcome in comparison to deceased donation with a mean graft survival benefit of 10 years.[8] For those patients who cannot directly receive a kidney from their living donor, inventive alternative programs for live kidney donation have been developed. Such programs include paired-kidney exchange,[9,10] unbalanced exchange donation,[11] unspecified donation, domino-paired exchange,[10,12,13] blood group AB0-incompatible transplantation,[14-16] and desensibilization of the sensitized recipient.[17]

Selection, screening, and informed consent of live kidney donors

Obviously, not everyone can donate a kidney. Ideally, living donors are carefully screened by several transplant professionals, consisting of nephrologists, transplant surgeons, anaesthesiologists, psychologists, social workers, and nurse practitioners. In some conditions, a cardiologist also evaluates the donor. Donors are extensively screened for several viruses, blood type, HLA type, kidney function and risk factors for future development of kidney disease. Prior to surgery, all donors undergo imaging (either a CT-scan or an MRI) to visualize the renal anatomy and parenchyma (to identify cysts or other anatomical variations). Based on this scan, a decision is made which kidney will be donated. Factors that are assessed on the scan are renal vascular multiplicity, renal artery stenosis, and the size and aspect of the kidneys.

With low complication and mortality rates, live donor nephrectomy is a safe, low-risk surgical procedure. In contrast to patients, living donors are (generally) healthy individuals in whom a vital organ is removed for the benefit of others. It is of the utmost importance that any individual is correctly informed about the specific details, risks, and alternatives of a procedure, but the unique character of the live donor nephrectomy may warrant an extra vigilant approach to the informed consent process.

In 2013, a European Union sponsored project, the 'Living Organ Donation in Europe ' (EULOD) project, current European practices in live organ donation were investigated, and found to differ significantly within Europe (and compared with the US).[18] Although the transplant community has established several international guidelines for the living kidney donor,[19-22] these guidelines differ regarding some statements. A uniform approach in the selection of live kidney donors is especially important since the community is seeking for options to further expand the donor pool. Currently, there is a tendency towards accepting so called 'extended criteria live kidney donors', which this thesis is about.

PART 1 – EXTENDED CRITERIA LIVE KIDNEY DONORS: REVIEW & ATTITUDES

Extended criteria live donors consist of potential kidney donors with one or more defined comorbidities, such as overweight or obesity, hypertension, older age, vascular multiplicity (the presence of more than one renal artery or vein), or donors known with (a history of) kidney stone-forming. Furthermore, the transplant community has not yet reached consensus regarding women of childbearing age and minors as potential donors. These criteria have been investigated in this thesis to give an overview of the outcome of these donors and retrieve a definite answer if they can safely be included in order to enlarge the donor pool. To systematically investigate current guidelines and literature, a systematic review was carried out regarding these extended criteria, which is presented in **chapter two** (**Aim #1**).
Although a systematic review can give an excellent overview of current literature, it is rather objective and moreover potentially subjective to publication bias. In **Aim #2**, to retrieve personal viewpoints of transplant professionals about the shifting paradigms in eligibility criteria; a survey was sent to members of the European Society for Organ Transplantation (ESOT), which is described in **chapter three**.

Furthermore, a very important aspect of living kidney donation, especially in the case of extended criteria donors, is the informed consent procedure prior to the operation. Since living donors are not patients, but healthy individuals undergoing an elective operation, the transplant community should provide optimal conditions and ensure donor safety. Although transplant professionals agree that consent should be voluntary, free of coercion, and fully informed, there is no consensus on which information should be provided, and how the donors' comprehension should be ascertained. In **chapter four,** we describe a systematic review that was carried out to reveal current practices regarding the informed consent procedure for live kidney donors around the world in order to eventually optimize and harmonize this procedure (**Aim #3**).

PART 2 – OBESITY IN LIVE KIDNEY DONATION

In most transplant centers, a body mass index (BMI) higher than 35 is considered a relative contraindication for donation. Because obesity increases the risk of complications after surgery in general, obese donors are also thought to be more prone for complications. However, in general, living donors consist of a highly selected group of healthy individuals and therefore cannot be compared with the general population regarding general health or comorbidities. Furthermore, long-term consequences of live kidney donation for this specific group are not yet fully clear. One can envisage a possible higher lifetime risk of hypertension, diabetes mellitus, or other morbidity. A possible solution for potential donors with morbid obesity could be bariatric surgery prior to donation. Several case reports have been published with good results.[23,24] In **chapter five, Aim #4** is presented; to reveal whether the BMI has influence on donor outcome, a systematic review and meta-analysis was carried out regarding the relation of BMI and outcome of laparoscopic donor nephrectomy.

Based on the results of chapter five, **Aim #5** was formulated, to find a potential better predictor for outcome of laparoscopic donor nephrectomy. Since the BMI does not take into account the fat distribution of a person, we investigated the role of perirenal and intra-abdominal fat mass in **chapter six**.

PART 3 – OBESITY IN RENAL TRANSPLANT RECIPIENTS

Kidney transplantation provides great benefit for patients with ESRD.[8] However, several important factors arise when selecting which patients will benefit and who will not. Obviously, any comorbidity that may endanger anaesthesia and surgery in general is a relative contraindication. Luckily, in most recipients, the technical feasibility poses no problem. Possible issues can be peripheral arterial occlusive disease, recurrent deep venous thrombosis, obesity, and previous abdominal surgery in general or hernia surgery using a mesh. Also, previous urological surgery is not uncommon in kidney transplant recipients. Not only in the population of possible live kidney donors, but the rising incidence and prevalence of increased body weight occurs in ESRD patients as well. As a consequence, the belief is that when these patients are transplanted, they are inherently more prone to complications. **Chapter seven** describes **Aim #6,** to reveal the role of the BMI in renal transplant recipients and their outcome, based on a systematic review and meta-analysis.

PART 4 – OTHER EXTENDED CRITERIA OF POTENTIAL LIVE KIDNEY DONORS

Several other extended criteria exist in the field of living kidney donation, amongst which vascular multiplicity. Vascular multiplicity means that a (donor) kidney has more than one renal artery and/or vein. Kidneys with multiple arteries are common in the general population and thus in potential live donors. Autopsy studies have suggested a prevalence of 18–30% for multiple renal arteries, with 15% being bilateral.[25,26] The presence of multiple renal arteries poses a challenge, because it may affect both donor safety and recipient outcome. This is because having multiple renal arteries may lead to intraoperative technical difficulties and complications, such as increased operative time, complicated dissection, or bleeding. Furthermore, either (arterial) reconstructions need to be created after extraction of the kidney or multiple arterial anastomoses are needed in the recipient, both associated with an increased risk for complications.[27] Because of the thought that donating a kidney with complex anatomy has an increased risk of the aforementioned complications for both the donor and the recipient, **Aim #7** was postulated. To investigate whether this assumption is just, in **chapter eight** we describe an analysis of the prevalence and respective outcome of vascular multiplicity in the cohort of the Erasmus MC, from 2006 to 2013.

Another phenomenon that can be qualified as an extended criterion is the presence of one or more kidney stones in a potential donor (nephrolithiasis). Annual incidence rates of kidney stones in the general population are approximately three cases per 1,000 individuals in men, and one to two cases per 1,000 individuals in women. The lifetime risk for kidney stone disease currently exceeds 6–12% in the general

population.[28] The global prevalence appears to increase steadily in both sexes and the latest numbers range between 1.7% and 14.8%.[29] One of the possible complications of kidney stones is an infection or obstruction, which leads to kidney damage.[30] **Chapter nine** presents **Aim #8**; to systematically review current available literature about the prevalence of kidney stones amongst live kidney donors and respective outcome of both the donors as well as their recipients. Furthermore, an analysis of the Erasmus MC cohort from 1994 until 2014 was added to reveal current practice regarding potential donors with stone-bearing kidneys and donor outcome after live donor nephrectomy and outcome of recipients following kidney transplantation.

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Chapter 2

Shifting Paradigms in Eligibility Criteria for Live Kidney Donation: A Systematic Review

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ABSTRACT

As the organ shortage increases, inherently the demand for donor kidneys continues to rise. Thus, live kidney donation is essential for increasing the donor pool. In order to create successful expansion, extended criteria live kidney donors should be considered. This review combines current guidelines with all available literature in this field, trying to seek and establish the optimal extended criteria. Comprehensive searches were carried out in major databases until November 2013 to search for articles regarding older age, overweight and obesity, hypertension, vascular anomalies/multiplicity, nulliparous women, and minors as donors. Of the 2079 articles found, 152 fell within the scope of the review. Five major guidelines were included and reviewed. Based on the literature search, live kidney donation in older donors (up to 70 years of age) seems to be safe as outcome is comparable to younger donors. Obese donors have comparable outcome to lean donors, in short- and mid-term follow-up. Since little literature is available proving the safety of donation of hypertensive donors, caution is advised. Vascular multiplicity poses no direct danger to the donor and women of childbearing age can be safely included as donors. Although outcome after donation in minors is shown to be comparable to adult donors, they should only be considered if no other options exist. We conclude that the analyzed factors above should not be considered as absolute contraindications for donation.

The incidence and prevalence of end-stage renal disease (ESRD) is rising globally as a result of an increased prevalence of hypertension, diabetes, obesity, higher age and other risk factors.[1] The best therapy for patients with ESRD is kidney transplantation. Not only does kidney transplantation reduce the risk of morbidity and mortality, it also improves quality of life compared with other forms of renal replacement therapy.[2,3] However, the number of deceased donors organs cannot meet the increasing demand.[4] Therefore live kidney donation has become increasingly important to enlarge the donor pool. Live donor kidney transplantation has superior graft outcome compared with deceased donor kidney transplantation, and is therefore the preferred therapeutic option for ESRD.[5] However, organ shortage remains, as not all transplant candidates have the luxury of a live donor.[4] Since the start of live kidney transplantation in the 1950s, the eligibility criteria for donation have been very strict and many risk factors, such as older age, overweight, obesity, hypertension, and vascular anomalies, were absolute contraindications for donation. During the past decades, there have been enormous developments in kidney donation. Experience with the assessment and evaluation of (potential) donors and technical aspects in this field has increased widely.[6-8] The outcome in donors and in recipients has proven to be excellent, leading to an extension of donor criteria in several transplant centers. Still, the local criteria for accepting live kidney donors vary greatly between transplant centers.[9] Furthermore, considerable variation is observed in the organization of live kidney donor evaluation and the methods of assessment used. With the increasing presence of certain risk factors and the shortage of kidney donors, the transplant community has made efforts to extend donor eligibility criteria to increase the live kidney donor pool. Hence, a shift has occurred in relative and absolute contraindications for live kidney donation.[10] Some contraindications for live donations are indisputable; however, controversy remains on some of the contraindications. The criteria for live kidney donation are elusive and differ worldwide, as well as nationally.[9] Thus, it is up to the transplant community, and the transplant teams in particular, to calculate the individual risk in each potential live kidney donor and set limits. However, as a consequence, many willing potential kidney donors with comorbidity, so called 'marginal live kidney donors', or 'extended criteria live kidney donors' are excluded in many transplant centers.

In this review, we searched for available guidelines and combined these to draw conclusions regarding the current attitudes on live kidney donor criteria. Furthermore, we examined available literature and evidence on extended living donor criteria regarding the controversial contraindications, such as older age, overweight and obesity, hypertension, vascular anomalies/multiplicity, women of childbearing age, and minors as donors. However, one must bear in mind that a live kidney donor should not become a patient. Even though technically a donation and successive transplantation might surgically not be a problem, the health of a donor must be the main priority at all times, surgical risks should be avoided at all costs, and good long-term outcome should be warranted.

RESULTS

We included five major available guidelines that are currently available in the field: the consensus statement of the Amsterdam Forum on the Care of the Live Kidney Donor,[11] the Summary of the British Transplantation Society/Renal Association UK guidelines for living donor kidney transplantation,[12] consensus guidelines on eligibility for kidney transplantation of the Canadian Society of Transplantation,[13] the Guidelines on Renal Transplantation by the European Association of Urology,[14] and the living kidney donors guideline Caring for Australasians with Renal Impairment (CARI) on obesity and hypertension were included.[15,16]

We also performed an extensive systematic literature search. Of the 2079 papers found after the initial search, 124 fell within the scope of the review. No additional studies were included after manually scrutinizing the reference lists. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for systematic reviews is presented in Figure 1. The assessment of the quality of the available evidence using the GRADE tool is presented in Figure 2.

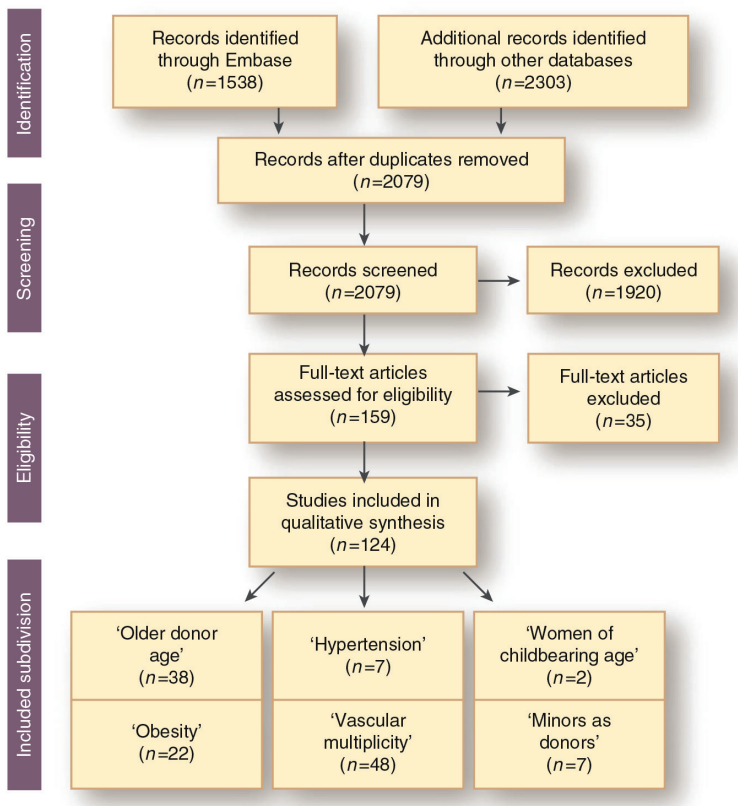

FIGURE 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart of the systematic literature search.

Live kidney donation of extended criteria live kidney donors

Patient or population: extended criteria live kidney donors
Settings: several extended criteria as listed below
Intervention: live kidney donation

Outcomes	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
Women of childbearing age Questionnaires Timing of exposure: 0–40 years[1]	23,325 (2 studies[2])	⊕⊖⊖⊖ Very low[3,4]	1814 cases and 22,015 controls in case–control studies
Hypertension Follow-up: 1–20 years[5]	81,497 (7 studies[6])	⊕⊕⊖⊖ Low	
Obesity Follow-up: 0–5 years[7]	5924 (22 studies[8])	⊕⊕⊖⊖ Low	
Older donor age Follow-up: 0–10 years[9]	90,027 (38 studies[10])	⊕⊕⊖⊖ Low	
Vascular multiplicity Follow-up: 0–10 years[11]	14,878 (48 studies[12])	⊕⊕⊖⊖ Low	
Minors as donors Follow-up: 40 years	347 (7 studies[13])	⊕⊖⊖⊖ Very low	

GRADE Working group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[1] Mean time of exposure of the two studies.
[2] Two case-control studies.
[3] Control groups consist of the general population.
[4] Some comparisons were made with the general population.
[5] Median follow-up of 5 years.
[6] Four retrospective cohort studies, two case studies, one review.
[7] Median follow-up of 12 months.
[8] Prospective cohort studies, nine retrospective cohort studies, two case-control studies, two systematic reviews.
[9] Median follow-up of 4.6 years.
[10] Prospective cohort studies, 16 retrospective cohort studies, five case-control studies, four case-series, one review.
[11] Median follow-up of 1.1 year.
[12] Prospective cohort studies, 43 retrospective cohort studies, one discussion.
[13] Retrospective cohort study, one case-series study, one case–control study, two surveys, two reviews.

FIGURE 2. Summary of findings table of extended criteria in live kidney donation generated by the GRADE tool.

Older donor age

Guidelines. No guidelines regarding maximum age for donation are available, nor are these included in the Amsterdam forum consensus in 2004,[11] the Canadian consensus guidelines,[13] and the CARI guidelines.[17] The British guideline states that older age alone is not an absolute contraindication for donation, but that the medical work-up of older donors must be particularly rigorous to ensure suitability. Donors older than 60 years should have a corrected glomerular filtration rate (GFR) of at least 68. This guideline also states that the older donor may have a greater risk of developing perioperative complications. This is particularly true for donors >60 years of age.[12] The Guidelines on Renal Transplantation by the European

Association of Urology mention that age limits for organ donation are not currently fixed, but lacks a recommendation for the maximum age for donation.[14]

Literature. Life expectancy in the Western population is rapidly increasing. In 2008, 17% of the European Union residents were 65 years or older. It is estimated that the population living in the European Union aged 65 years and older will increase by 70% in 2050, and the number of octogenarians is expected to increase by 170%.[18] This trend will lead to an increase in the incidence and prevalence of ESRD. At the same time, this age group may also be considered a source for live donor kidney transplantation. Raising the maximum age for live kidney donation will result in more donors, but using older donors for live kidney transplantation still remains controversial.

Donors aged 60 – 70 years

Segev *et al.*[19] observed no significant difference in perioperative mortality for different live kidney donor age groups. Donors aged 50-59 years (hazard ratio (HR) 3.3; 95% confidence interval (CI) 2.6-4.1) and donors aged 60 years or older (HR 9.4; 95% CI 7.3-12.1) were associated with a greater 12-year mortality rate when compared with donors aged 18-39 years (HR 1). However, long-term mortality was similar or lower for live kidney donors in comparison with the healthy matched nondonor control cohort throughout the 12-year follow-up period (1.5 vs. 2.9%; $P<0.001$). Thus, no evidence was found that live kidney donors older than 50 years have an increased risk of mortality after donation. O'Brien *et al.*[20] determined whether acceptance of elderly and obese living kidney donors was associated with a greater perioperative risk and long-term complications. Therefore, kidney donors were divided into groups, consisting of elderly donors, obese donors, elderly and obese donors, and a reference group. O'Brien *et al.* demonstrated no significant differences in operative time, length of hospital stay, estimated blood loss, and rate of early postoperative complications between two groups of older live kidney donors (62.0 ± 1.5 and 68.2 ± 2.6 years) and a reference group of younger live kidney donors (42.3 ± 10.4 years). Renal function parameters showed a significant decrease after donation, but variation between the groups was not significant when compared with the reference group ($P>0.28$). Major complications and mortality rates were absent in the groups. Jacobs *et al.*[21] demonstrated that donor nephrectomy may be performed safely in live kidney donors older than 60 years of age. There were no significant differences between the older (>60 years) and younger (<40 years) live kidney donors with regard to operative time (210.2 ± 51.2 and 201.7 ± 55.1 min, respectively), warm ischemia time (195.6 ± 99.8 and 170.3 ± 95.9 s, respectively), and estimated blood loss (157 ± 266 and 112 ± 121 ml, respectively). Intraoperative and postoperative complication rates were also equivalent between older and younger live kidney donors. In all, 9.5% of donors older than 60 years experienced intraoperative complications, a similar rate as in donors younger than 40 years, according to the authors (21%). Postoperative complications occurred in 21% of the elderly donors and in 11.9% of the younger donors, respectively. Furthermore, there was no increased length of hospital stay for the older live kidney donors, and serum creatinine levels during the postoperative hospital stay were identical. In a systematic review by Young *et al.*[22], no significant differ-

ences were found between the younger and older donors, most commonly defined as older than 60 years, when comparing operative time (*P*=0.11), blood loss (*P*=0.90), and length of hospital stay (*P*=0.83). Klop *et al.* quantified the effect of the surgical procedure on the quality of life of elderly donors ≥ 60 years compared with younger donors. Their findings demonstrate that elderly donors recover relatively fast. In a different study, Klop *et al.*[23] also demonstrated that the prevalence of incisional hernias after live donor nephrectomy is very low, and body image and cosmetic scores are excellent. The mean age in the elderly group was 66 years, as compared with 45 years in the younger group. Body mass index (BMI) (mean 26.0 kg/m^2 in both groups), type of operation (open in 25% vs. 23%), postoperative complication rate (10% and 9%) and length of hospital stay (median 3 days in both groups) did not differ between groups. One month postoperatively, inter-group analysis showed a significant advantage in quality of life in favor of the elderly group regarding the SF-36 dimensions 'bodily pain''role physical' and 'vitality'. At 3 months, 'bodily pain' and 'role physical' were still in favor of the older group. At 6 and 12 months, 'physical function' was in favor of the younger group.[24] Dols *et al.*[25] demonstrated that median estimated blood loss was significantly higher (230 (0-1285) vs. 180 (0–3000) ml; *P*=0.011) and median warm ischemia time significantly shorter (4 (1–13) vs. 5 (1-20) min; *P*=0.024) in live kidney donors ≥ 60 years, when compared with donors < 60 years. Moreover, live kidney donors in the older group had a significantly longer median length of hospital stay (4 (2–15) vs. 3 (1–31) days; *P*=0.012). The rates of minor and major intraoperative and postoperative complications did not differ significantly between the two groups. The older live kidney donors had a lower GFR before donation, but there were no significant differences in GFR decline between the two groups. Five years after donation, significantly more of the older live kidney donors had a GFR < 60 ml/min compared with the younger live kidney donors (131 (80%) vs. 94 (31%); *P*<0.001), but renal function was stable and no GFR of less than 30 ml/min was observed. Some other studies also recommend that healthy older-aged donors should not be turned down because they do not seem to have a greater risk of intraoperative and postoperative complications. Furthermore, long-term follow-up data show good outcomes for donors of older age.[26-53] Thus, live kidney donation by older donors may be considered safe, as the complications after donation are limited and GFR does not progressively decline, at least not during relatively short-term follow up (median follow-up: 5.5 years). Multiple other, smaller studies showed similar results.[54-56] Recently, Hourmant *et al.*[57] published that despite reduced renal function of an old kidney, the results of transplantation from an old living donor appeared to be equivalent to deceased transplantation from a younger donor. Finally, transplantation from an old living donor appeared to be a reasonably safe procedure for both the donor and the recipient, and age alone is certainly not a contraindication for donation.

Donors over 70 years of age

The majority of elderly donors described in the aforementioned studies are between 50 and 70 years old. Older age has a wide age range. A subdivision in these older-age categories will provide a clear overview of the currently available data concerning the safety of donation in these specific age populations. Berger *et al.*[56] studied the outcome of living kidney donors aged 70 years and older. A total of 219 healthy

adults aged older than or equal to 70 years donated a kidney. Competing risk models with matched controls were used to study the independent association between older donor age and donor survival. Survival among live donors aged 70 years was 95.8% (95% CI 91.4-98.1%) at 5 years and 90.0% (95% CI 83.5-94.0%) at 10 years. Among matched nondonor controls from the general population, survival was 91.8% (95% CI 87.3-94.7%) at 5 years and 73.0% (95% CI 65.6-79.0%) at 10 years. Mortality among live kidney donors aged 70 years and older was no higher than that in healthy matched controls drawn from the National Health and Nutrition Examination Survey III (NHANES-III) cohort; in fact, mortality rates were lower, probably reflecting greater selectivity among older live donors than could be captured in NHANES-III (HR 0.37, 95% CI 0.21-0.65, $P<0.001$). These findings support that live donation among donors aged above 70 years is safe. The study of Dols *et al.*,[25] as mentioned before, included 25 (5%) donors of 70 years or older. The mean age in this group was 74 (74-90) years. No significant differences in operative time, complications, conversions, or development of hypertension were observed in comparison with the group younger than 70 years. However, hospital stay was significantly longer for donors aged 70 years or older (5 vs. 4 days, $P<0.001$), possibly explained by the social conditions needed to offer these donors adequate care in their home situation. Ivanovski *et al.*[44] presented their 20-year experience with 230 living donor renal transplantations using elderly individuals, with 90 of them being older than 65 years, and a mean age of 68 ± 4.5; (range 65-86 years). There were no significant surgical complications among the kidney donors. Their findings confirmed that donor nephrectomy is a safe procedure even in donors over 65 years of age.

Little data are available related to live kidney donation in donors older than 70 and 80 years. This is due to the fact that many previous studies generalized 'older donors' as donors over 60 years, and a subdivision in older ages is generally not made. Moreover, some transplant centers are reluctant selecting donors over 70 years or even 80 years of age.[9] Another limitation for excluding donors older than 70 years is fear of delayed graft function by transplant physicians.[58,59]

Recommendation. We conclude that an older age (at least up to the age of 70) is no contraindication for living kidney donation. Little data are available about live kidney donors aged over 70 or 80 years. However, data that are available for these specific donors show that donor nephrectomy is a safe procedure and survival of donors is comparable to that of general populations. Besides the fact that older age does not seem to have a negative impact on the outcome after donor nephrectomy, it is not necessarily actual age itself, but renal function, the presence of other comorbidities, and overall health that will determine whether an older live kidney donor should be included or excluded. In other words, biological age rather than actual age seems to be important. A current view is that a possible impaired renal function and health after donor nephrectomy may be considered more acceptable for older than for younger live kidney donors. The largest prospective follow-up study reporting on the quality of life of the donor was conducted by Klop *et al.*[60] It demonstrates that the elderly donor had an advantage in three of the four end points during the follow-up and that the quality of life is comparable between

donor groups. This perspective of excellent postoperative quality of life may actually convince older people to donate.[60]

LEVEL OF EVIDENCE FOR THIS EXTENDED CRITERION:

Level 1: 2%	**Level 4: 2%**
Level 2: 23%	**Level 5: 0%**
Level 3: 74%	**Grade of recommendation: B**

Obesity

Guidelines. The British guidelines recommend that otherwise healthy overweight patients (BMI 25-30 kg/m^2) may safely proceed to kidney donation. Moderately obese patients (BMI 30-35 kg/m^2) should undergo careful preoperative evaluation to exclude cardiovascular, respiratory, and kidney disease. The guidelines also suggest that as data on the safety of kidney donation in the very obese (BMI>35 kg/m^2) are limited, such individuals should be discouraged from donating.[12] The CARI guidelines consider obesity (BMI>30 kg/m^2) a relative contraindication to donation.[15] In addition, potential donors who are obese should be very carefully assessed for risk factors associated with chronic kidney disease. These include impaired glucose tolerance, hypertension, and proteinuria. The presence of obesity and a second risk factor should be considered a contraindication to donation. The Canadian guideline does not provide any recommendations concerning obese donors, neither does the European Association of Urology.[13,14]

Literature. A BMI>35 kg/m^2 is considered a relative contraindication for live kidney donation.[9] In the general population, obesity is associated with proteinuria and hypertension, and may lead to ESRD.[10,61] Praga *et al.*[62] studied obesity as a potential risk factor for renal insufficiency after nephrectomy for reasons other than donation. Long-term follow-up demonstrated a correlation between the development of proteinuria and some level of renal insufficiency with a BMI>30 kg/m^2. The question remains whether this is also applicable to donors with obesity. The following consensus guidelines regarding obesity were adopted at the International Forum for the Care of the Live Kidney Donor held in Amsterdam in 2004:[11] Individuals with a BMI>35 kg/m^2 should be discouraged from donating, especially when other comorbidities are present.

- Obese individuals should be encouraged to lose weight prior to kidney donation and should be advised not to donate if they have other associated comorbidities.
- Obese individuals should be informed of both acute and long-term risks, especially when other comorbidities are present.

Healthy lifestyle education should be available to all living donors. A recent survey in the UK showed that there is an inconsistency in accepting donors with a BMI>30 kg/m^2.[63]

Tavakol *et al.*[64] showed that obese live kidney donors (BMI≥30 kg/m^2) have no increased risk of reduced renal function after donation when compared with nonobese live kidney donors (BMI<30 kg/m^2), but that there is an increased risk of developing hypertension (odds ratio 4.02; 95% CI 1.20-13.00; *P*=0.021) and other risk factors for cardiovascular disease, such as abnormal high-density lipid cholesterol levels (odds ratio 4.5; 95% CI 1.3-15.0; *P*=0.015), at a mean follow-up of 11 years. However, when donors were compared with BMI-matched two-kidney control subjects to determine whether this increase was due to nephrectomy, obesity, or a combination of both, the rates of hypertension and lipid abnormalities in obese donors were similar to the rates observed in the obese two-kidney control subjects. Two-kidney control subjects were matched with donors for current BMI, current age, race, gender, diabetes, and smoking history. Individuals with known renal disease and other significant medical comorbidities, with the exception of hypertension and dyslipidemias, were excluded. This suggests that the increased risks were attributable to obesity rather than the nephrectomy itself. O'Brien *et al.*[20] showed that operative time, estimated blood loss, and length of hospital stay were not significantly increased in obese live kidney donors (BMI 31.9 ± 1.2 and 38.0 ± 3.4 kg/m^2) in comparison with non-obese live kidney donors (BMI 24.9 ± 2.8 kg/m^2). Early postoperative complication rates were not significantly different, although subgroup analysis demonstrated a higher incidence of respiratory complications at the extremes of obesity (BMI ≥ 40 kg/m^2), with 57% of these donors requiring antibiotic therapy for suspected pneumonia (*P*<0.01). On follow-up, renal function parameters showed significant changes post-nephrectomy, but variation between all groups was not significant when compared with the reference group (*P*>0.28). Heimbach *et al.*[65] found an increased risk of minor surgical complications, especially wound complications, in obese live kidney donors (BMI 30-34.9 and BMI≥35 kg/m^2) when compared with nonobese live kidney donors (BMI<25 kg/m^2) (11 (10%), 5 (9%), and 4 (2%) donors, respectively (*P*<0.05)). The rate of major surgical complications was low and comparable in all groups of live kidney donors, and a similar length of hospital stay was observed. Operative times were significantly longer for obese live kidney donors. At 6 to 12 months after donation, renal function and microalbuminuria did not differ according to BMI. Reese *et al.*[66] reported that live kidney donors with an increased BMI have higher mean blood pressures at baseline and after nephrectomy, but that changes in blood pressure were not related to BMI. Higher donor BMI at baseline did not increase the risk of reoperation, readmission, vascular or other complications, or increase the length of hospital stay. At six months follow-up, the relative changes in donor serum creatinine and GFR were similar across BMI groups (*P*=0.62). Differences in mean absolute estimated GFR across BMI groups, although statistically significant, were not clinically important (62.0 ml/min per 1.73 m^2 for normal-weight donors (BMI<25 kg/m^2) vs. 59.9 for overweight donors (25≤BMI<30 kg/m^2), 60.6 for obese donors (30≤BMI<35 kg/m^2), and 62.7 for very obese donors (BMI≥35 kg/m^2); *P*<0.01) and did not rise consistently across BMI categories (*P*=0.62). Young *et al.*[22] showed that intraoperative outcomes including operative time and estimated blood loss were marginally increased in obese groups, where the pooled estimate of the mean increase in blood loss amounted to 57 ml and that of operative time to 20 min. Recently, we published a systematic review and meta-analysis of the aforementioned studies and the current literature regarding perioperative outcome of live donor

nephrectomy between high and low BMI donors (≥30 vs. ≤ 29.9 kg/m^2).[67] Significant differences were found in favor of low-BMI donors (≤29.9 kg/m^2): a difference in mean operation duration of 16.9 min (CI 9.1-24.8; *P*<0.0001), a difference in mean rise in serum creatinine of 0.05 mg/d; (CI 0.01-0.009; *P*=0.02), and a risk ratio for conversion of 1.69 (CI 1.12-2.56; *P*=0.01). No significant difference in warm ischemia time, blood loss, length of hospital stay, the number of perioperative complications (such as bleeding, conversion, wound complications, urinary tract infections, readmission, and reoperation), and change in GFR were found. In a subanalysis, no significant difference in aforementioned outcome measures were found between kidney donors with a BMI of 30-34.9 kg/m^2 compared with those with a BMI of 35 kg/m^{2}and higher. The authors conclude that regarding short-term outcome a high BMI itself should not be a contraindication for live kidney donation. Various other studies have reported on the feasibility of live kidney donation from obese donors.[33,68-79]

Recommendation. On the basis of the available literature, we conclude that the selection of potential kidney donors should not be based on BMI alone. A high BMI, irrespective of its actual value, should not be considered as an absolute contraindication for living kidney donation. The transplant community should carefully screen each individual obese donor for other comorbidities and make a selection based on those results. Donation in obese living kidney donors appears to be safe. However, the selection for donation by an obese potential donor should be a careful individualized process, where all possible comorbidities must be carefully interpreted. The most important factor is the pretransplant renal function and, obviously, the reserve capacity of the remaining kidney. The donors' health should always be prioritized, especially in this selective group, as data on long-term renal function of obese donors are scarce. In addition, counseling should be provided to control weight, and appropriate medical follow-up should be maintained after donation. Worldwide consensus is that all individuals with a BMI>40 kg/m^2 (regardless of a wish for donation) should be considered to undergo bariatric surgery.[80] Furthermore, we advocate bariatric surgery for all potential donors with a BMI>40 kg/m^2, in which standard dietary restriction results in insufficient weight loss. One must bear in mind that long-term follow-up of obese renal donors is limited, as obesity has been considered a relative contraindication to donation until now. Therefore, little evidence is available regarding obese individuals with comorbidities such as hypertension or older age, who have donated their kidney.

LEVEL OF EVIDENCE FOR THIS EXTENDED CRITERION:

Level 1: 10%	**Level 4: 10%**
Level 2: 5%	**Level 5: 0%**
Level 3: 75%	**Grade of recommendation: B**

Hypertension

Guidelines. Hypertension (defined as blood pressure > 140/90mmHg)[81] has been considered to be a contraindication for live kidney donation, but the exact risk for donors with a raised blood pressure has not yet been determined. Guidelines regarding hypertensive donors were adopted at the aforementioned forum in Amsterdam in 2004.[11] These guidelines recommend the following: Patients with a blood pressure >140/90 by ambulatory blood pressure monitoring (ABPM) should generally not be accepted as donors; blood pressure should preferably be measured by ABPM, particularly among older donors (>50 years) and/or those with high office blood pressure readings; some patients with easily controlled hypertension who meet other defined criteria (e.g., >50 years of age, GFR>80 ml/min, and urinary albumin excretion <30 mg/day) may represent a low-risk group for the development of kidney disease after donation and may be acceptable as kidney donors; donors with hypertension should be regularly followed up by a physician. The British guidelines recommend that potential donors with blood pressure <140/90mmHg should be considered as normotensive and therefore suitable for donation on the basis of blood pressure. The presence of mild-moderate hypertension that is controlled with 1-2 antihypertensive agents is not a contraindication to donation, provided that significant end-organ damage has been excluded. Last, they recommend that evidence of hypertensive end-organ damage, poorly controlled hypertension, or hypertension that requires more than two drugs to achieve adequate control are relative contraindications to donor nephrectomy.[12] The CARI guidelines consider elevated blood pressure above 140/90mmHg as a relative contraindication for donation.[16] Donors with evidence of end-organ damage related to hypertension, for example retinopathy, left ventricular hypertrophy, proteinuria, or poorly controlled hypertension (requiring more than two agents), should not be considered for donation. The Canadian guidelines do not include recommendations regarding hypertensive donors.[13] The European Association of Urology only states that uncontrolled hypertension is an absolute exclusion criterion of these potential living kidney donors.[14]

Literature. To date, few articles have been published regarding the outcome of accepting hypertensive live kidney donors for donation. Segev *et al.*[19] showed that hypertension in live kidney donors was associated with an increased mortality rate within 3 and 12 months after donor nephrectomy (risk ratio 27.4; 95% CI 5.0-149.5; *P*<0.001), although this was solely based on a small number of donors among the total donor population with hypertension. Therefore, the magnitude of the excess risk remained uncertain. In addition, a systolic blood pressure of 120-139 or ≥140mmHg was associated with higher 9-year mortality rates when compared with a systolic blood pressure of less than 120mmHg (HR 1.2; 95% CI 0.8-1.6; HR 1.7; 95% CI 1.1-2.9, respectively). Long-term risk of mortality was not higher for live kidney donors than for a healthy matched nondonor control cohort throughout the 12-year follow-up period (1.5 vs. 2.9%; *P*<0.001). Textor *et al.*[82] showed that hypertension in live kidney donors (awake ABPM 142 ± 3/85 ± 2mmHg, clinic blood pressure 155 ± 3/88 ± 2mmHg and nurse blood pressure 136 ± 3/78 ± 2mmHg) with otherwise normal GFR and protein excretion has no measurable adverse effects on the donor during the first year after nephrectomy regarding blood pressure, GFR, serum creatinine, urinary

protein excretion, and urinary microalbumin. Tent *et al.*[83] demonstrated that hypertensive live kidney donors (awake ABPM 139 ± 16/82 ± 10mmHg) show a similar course in postdonation renal function and blood pressure when compared with normotensive donors (awake ABPM 129 ± 12/77 ± 8mmHg), and that hypertensive donors do not have an increased risk of renal function loss up to 5 years after donation. Young *et al.*[22] compared live kidney donors with hypertension with donors without hypertension. The results regarding the decrement in GFR after donor nephrectomy were conflicted, substantially heterogeneous, and not pooled (a mean difference in GFR decrement between hypertensive and normotensive donors of 4 ml/min per 1.73 m^2 (95% CI -1 to 10) vs. a mean difference of -8 (95% CI -12 to -4)). Hypertension in live kidney donors was also not associated with a greater increase in blood pressure after donor nephrectomy. Rather, blood pressure appeared to decrease more in hypertensive than in normotensive donors after donation. Some other studies reported positive outcome on including hypertensive donors.[38,84-86]

Recommendation. Hypertension should remain a relative contraindication for live kidney donation. Hypertensive live kidney donors with a blood pressure of approximately 140/90mmHg, established by 24-h ambulatory blood pressure measurement (ABPM) and normal renal function, show similar postdonation blood pressure and renal function as normotensive living kidney donors. However, based on the evidence available, the exact degree of hypertension and renal function has not yet been established. In general, the manageability of the hypertension, the presence of other comorbidities and overall health determine whether individuals with hypertension should be included or excluded as live kidney donors. These conclusions are also in accordance with the consensus guidelines that were adopted at the Amsterdam Forum in 2004, further stressing the importance of observing these guidelines among transplant centers.[11]

LEVEL OF EVIDENCE FOR THIS EXTENDED CRITERION:

Level 1: 12.5%	**Level 4: 12.5%**
Level 2: 0%	**Level 5: 0%**
Level 3: 75%	**Grade of recommendation: B**

Vascular multiplicity

Guidelines. Surprisingly, no guidelines regarding live kidney donors with multiple renal arteries or veins are available and stated in the consensus of the Amsterdam Forum in 2004, whereas some centers repeatedly exclude live donor kidneys with more than one artery.[87] With regard to this matter, the British guidelines state that multiple renal arteries or kidneys with anatomical anomalies are not absolute contraindications to donation. Decisions should be made on an individual basis as part of a multidisciplinary team meeting.[12] They also state that multiple renal arteries are associated with an increased incidence of complications in the recipient. Again, the Canadian guidelines, the guidelines of the European Associa-

tion of Urology, and the CARI guidelines do not propose any recommendations concerning arterial or venous multiplicity.[13,14,16]

Literature. Kidneys with multiple arteries are common in the general population and thus in potential live donors. Autopsy studies have suggested a prevalence of 18%-30% for multiple renal arteries, with 15% being bilateral.[88,89] The presence of multiple renal arteries presents a challenge, because it may affect both donor safety and recipient outcome. This is because having multiple renal arteries may lead to intraoperative technical difficulties and complications, such as increased operative time, complicated dissection, or bleeding. Furthermore, either (arterial) reconstructions need to be created after extraction of the kidney or multiple arterial anastomoses are needed in the recipient, both associated with an increased risk for complications.[90] One other study reported on ureteral complications in recipients after donor nephrectomy of kidneys with multiple vessels.[91] Ureteral complications occurred in 6 of 36 (17%) recipients of kidneys with reimplanted accessory arteries compared with 10 of 312 (3%) control recipients and 1 of 13 (8%) recipients of kidneys with ligated accessory arteries (P=0.0013). Kok *et al.*[92] showed that accessory arteries to the lower pole correlated with an increased rate of ureteral complications (P=0.01). These complications consisted of one distal ureteral necrosis because of thrombosis of the inferior pole accessory vessel, and one other patient developed a ureteral stricture 10 days following transplantation. Several studies have been conducted in the past decade regarding the outcome of renal artery multiplicity in live donors.[93-98] Desai *et al.*[93] observed that, when compared with live donors with a single renal artery, live donors with two renal arteries and donors with early branching had a significantly longer graft retrieval time (3.9 ± 1.4 and 3.9 ± 0.8, respectively, vs. 3.5 ± 1.0 min; P=0.03 and P=0.01, respectively) and longer operative time (166.3 ± 49.1 and 162.4 ± 41.5, respectively, vs. 147.6 ± 44.1 min; P=0.02 and P=0.04, respectively). However, all donors were equivalent in terms of postoperative analgesia usage and length of hospital stay. Intraoperative and postoperative complications did occur, but none of the complications were related to the number of vessels. In addition, no bleeding complications were observed in donors with multiple vessels. Although the serum creatinine level was higher in the multiple-vessel group at 1 day, at 1 month and 1 year, the difference was not statistically significant. Moreover, the overall graft outcome was similar in all groups, implying low clinical relevance. Paragi *et al.*[98] observed no significant difference in postoperative serum creatinine (P<0.31), mean estimated blood loss (P<0.75), complication rate (P>0.99), or length of hospital stay (P<0.28) between single and multiple-artery donor kidneys. Only operative time was significantly different between the two groups in favor of the donors with a single artery (119 ± 43 vs. 128 ± 40 min; P<0.01). On the contrary, Hsu *et al.*[99] showed that the presence of multiple renal arteries was not associated with a significantly longer operative time: the comparison between donors with one and two renal arteries showed no significant difference in mean total operative time (P=0.14), as well as the comparison between donors with one and three renal arteries (P=0.65) and two and three renal arteries (P=0.74). Moreover, no relation was found between the number of renal arteries and estimated blood loss, complication rate, and length of hospital stay. In addition, more studies demonstrate that arterial multiplicity is not a contraindication

to donation.[87,93,94,100-133] Besides renal artery multiplicity, vascular anomalies may also concern venous anomalies. Whereas most studies concern the impact of multiple renal arteries only, in 2008 Fettouh *et al.*[97] also included donors with venous anomalies. They demonstrated that when comparing the results of live kidney donors with vascular anomalies with donors without vascular anomalies, only operative time was significantly increased in donors with vascular anomalies (161 ± 35 vs. 131 ± 26 min; $P<0.05$). No significant differences were observed in estimated blood loss, hospital stay, and readmission.

Recommendation. Vascular anomalies (in particular arterial multiplicity up to 3 renal arteries) should not be a contraindication for live kidney donation. The presence of multiple renal arteries or veins may present a challenge to the donor's surgeon, but inherent longer operative times have no negative impact on outcome of the donor after living donor nephrectomy. With modern surgical techniques and high surgical skills, neither renal artery multiplicity nor venous anomalies seem to pose any significant danger to the living kidney donor. With the optimization of the preoperative imaging nowadays (specifically CT scans), we are able to meticulously define the anatomy and therefore can choose the kidney with the least complex vascular anatomy. During the early years of the donor nephrectomy, preoperative angiography was used. In the following years, MRI was introduced; however, both were considered suboptimal in the more complex anatomical cases.[92] Nowadays, in most centers, the CT scan is a gold standard and is considered to be more sensitive in correctly assessing the complex vascular anatomy.[134-136]

A small accessory artery that supplies a minor part of the upper pole (subjectively assessed using predonation CT scans) can be safely sacrificed.[137] However, an accessory artery that vascularizes the lower pole and inherently the proximal part of the ureter must be saved and reconstructed after nephrectomy. Ali-El-Dein *et al.*[119] proved that bench surgery is as effective as intracorporeal reconstruction of the anastomosis of multiple renal arteries with no increase in the incidence of relevant complications for the recipient.

Nevertheless, it should be noted that most living donors with multiple renal arteries in the reported studies were donors with a maximum of three renal arteries.[47,92,93,95-99,111-113,115,116,118-123,126,128,129,131] Only a minority of the donors with multiple renal arteries had four or more renal arteries.[92,93,95,98,112,113,119,121-123] Moreover, as no literature is available on donors with more than four renal arteries, we cannot draw any definitive conclusions in this regard. Thus, the results from these studies are probably best applied to living donors with up to three renal arteries.

LEVEL OF EVIDENCE FOR THIS EXTENDED CRITERION:

Level 1: 0%	**Level 4: 5%**
Level 2: 2%	**Level 5: 0%**
Level 3: 93%	**Grade of recommendation: B**

Women of childbearing age as potential donors

Guidelines. The Amsterdam Forum Guidelines state that donor nephrectomy is not detrimental to the prenatal course or outcome of future pregnancies. It is recommended, however, to delay pregnancy until at least 2 months after nephrectomy to assess renal compensation prior to conception, with evaluation including blood pressure, GFR, and assessment for microalbuminuria. The British Guidelines state that the presence of a solitary kidney does not appear to pose a significant risk during the course of a normal pregnancy, and outcomes for pregnant kidney donors are considered comparable to those in the general population. Other guidelines give no statements regarding this subject.

Literature. Ibrahim *et al.*[138] published a large survey in 2009 of 2102 women who had donated a kidney, in which fetal and maternal outcomes and pregnancy outcomes after kidney donation were similar to those reported in the general population. However, postdonation pregnancies were associated with a lower likelihood of full-term deliveries compared with predonation pregnancies (73.7% vs. 84,6%, P=0.0004) and a higher likelihood of fetal loss (19.2% vs. 11.3%, P<0.0001). Furthermore, postdonation pregnancies were also associated with a higher risk of gestational diabetes, gestational hypertension, proteinuria, and preeclampsia (all P<0.0001). In 2009, Reisæter *et al.*[139] published that in 326 donors the occurrence of preeclampsia was more common in pregnancies after donation (5.7% vs. 2.6%, P=0.026). No differences were observed in the occurrence of adverse pregnancy outcome in kidney donors compared with the general population.

Recommendation. On the basis of the literature that is available on this topic, there is no evidence to conclude that women of childbearing age should be declined as potential kidney donors. However, one must bear in mind that comparison with the general population may be prone to confounding, because live kidney donors are generally considered to be in better health. Most importantly, the effects of donation on maternal and fetal outcomes should be part of the routine discussion about the risks of donation during the informed consent procedure.

LEVEL OF EVIDENCE FOR THIS EXTENDED CRITERION:

Level 1: 0%	**Level 4: 100%**
Level 2: 0%	**Level 5: 0%**
Level 3: 0%	**Grade of recommendation: C**

Minors as kidney donors

Guidelines. The Amsterdam Forum Guidelines state that with the excellent outcome of specified live donor kidney transplantation using adult donors that are genetically unrelated, minors less than 18 years of age should not be used as living kidney donors. The British Guidelines state that the moral arguments for not subjecting young people, under the age of 18 years, to the rigors of living kidney donation are

compelling and minors should rarely, if ever, be considered as potential living donors. However, some regard the use of an identical twin as an acceptable child donor, on the basis that the outcome for the recipient twin is exceptional and because the relationship between identical twins is so close that restoring the health of the recipient confers major psychological benefit for the donor.[140] This view is highly controversial and has been challenged.[141,142]

Literature. In 1997, Spatel *et al.*[143] performed a survey amongst 117 US transplant centers. The great majority of responding centers (68%) required living donors to be at least 18 years old. They state that in unusual circumstances in which no other suitable donor is available, consenting mature minors, and even rare immature minors who are highly likely to benefit from donating, may be ethically acceptable. In 2002, Delmonico *et al.*[144] performed an analysis of the UNOS database and concluded that a minor may ethically act as a live organ donor: when the potential donor and recipient are both highly likely to benefit (as in the case of identical twins); when the surgical risk for the donor is extremely low; when all other opportunities for transplantation have been exhausted; when no potential adult living donor is available, and timely and/or effective transplantation from a cadaver donor is unlikely; and when the minor freely agrees to donate without coercion (established by the independent donor advocate). Recently, Thys *et al.*[145] published a systematic review about this topic, combining all available guidelines, publications, and reports. They conclude that 27 out of 39 'guidelines' endorse a prohibition of living kidney donation by minors. In contrast, 12 guidelines exceptionally allow living kidney donation by minors, provided that adequate safeguarding mechanisms are present. These include an assessment of the minor's decision-making capacity and best interests by an independent competent body. MacDonald *et al.*[146] recently showed that, during long-term follow-up (mean 31.6 years), pediatric donors do not have a greater risk of developing hypertension or diabetes and have a significantly lower risk of developing an estimate GFR <60.

Recommendation. We recommend that minors (aged <18 years) should not be considered as kidney donors, except in rare cases where no other options are available for the recipient.

LEVEL OF EVIDENCE FOR THIS EXTENDED CRITERION:

Level 1: 0%	**Level 4: 87.5%**
Level 2: 12.5%	**Level 5: 0%**
Level 3: 0%	**Grade of recommendation: C**

General conclusions. The transplant community's attempt to extend donor eligibility criteria has led to a shift in accepting live kidney donors with more comorbidities over the years. The main concern with this trend is the safety of the potential live kidney donor and the outcome of the recipient. Furthermore, there is a lack of international consensus. This accounts for the (in some cases major) differences in donor

criteria between transplant centers. Four of the most common comorbidities discussed in our review are considered to be a contraindication for donation.

As pointed out before, the most important aspect in selecting possible live kidney donor is their safety. A live kidney donor is generally in good health. The transplant community should be aware of this fact and realize that the donor should not become a patient. Moreover, because the donor does not directly benefit from the procedure, especially this particular group should be treated with the best medical attention. In the current era, in which efforts are made to increase the donor pool by increasingly accepting extended criteria donors, we should be extremely careful in the selection process.

Few similar studies are conducted regarding these comorbidities to live kidney donation. The United Kingdom has established guidelines regarding the majority of comorbidities to live kidney donation in May 2011.[12] The UK guidelines are in concordance with the findings of this review regarding older age, overweight/obesity, hypertension, and vascular anomalies. Serur *et al.*[147] conducted a similar study on the available data on high-risk donors and the appropriateness of accepting them as live kidney donors. However, in this review, we focused on the most controversial donor criteria for acceptance. We performed a systematic review, including all available literature, and thereby studied the outcome in a comprehensive donor population with an extensive follow-up duration, aiming to establish the optimal criteria for safe live kidney donation regarding these extended donor criteria.

Limitations. Even though our findings support the inclusion of donors with older age, obesity, hypertension, vascular anomalies, and women of childbearing age for live kidney donation, one needs to bear in mind that the long-term outcome (longer than 20 years) for these donors has yet to be established. Moreover, some of the studies that concern the outcome of extended eligibility criteria for the live kidney donor have limitations, such as single-center experience, retrospective study design, small sample sizes, and non-matched cohorts. It is important to remain cautious when drawing hard conclusions from these studies regarding the extended live kidney donor criteria. In this respect, again, we also like to emphasize the importance of long-term follow-up. Furthermore, regarding older donors, little data are available regarding the age groups of older than 70 or even 80 years. Although we conclude that older age in itself is no contraindication, careful consideration is warranted regarding the upper age ranges.

In this systematic review, we have assessed a number of individual extended criteria. However, the transplant community should be aware that in the future an increasing number of potential donors will have more than one extended criterion. Although one specific criterion can be harmless, a combination of several criteria could pose a problem regarding donor safety, both in short-term and long-term consequences. By conducting this review, we did not create any insight in this important issue.

Another important point is the scoring of the evidence. Although the GRADE method is a great tool to score the level of evidence, regarding our extended criteria, no randomized controlled trials can

be performed. Thus, all available literature are observational studies, automatically resulting in a lower evidence scale. This is one of the reasons why also the Oxford Level of Evidence scale is included.

Despite the limitations in currently available literature, we conclude that older age, obesity, hypertension, vascular anomalies, and women of childbearing age are no absolute contraindications for live kidney donation. Accepting donors with these conditions has great potential in diminishing the kidney donor shortage. With regard to contraindications for live kidney donation, it must be emphasized that every potential donor should be approached individually and that no generalizations should be made. It is of utmost importance, as mentioned above, that potential risks for the donor should be avoided. Another important aspect in our opinion is the experience of the transplant team and inherent center volume. It should be emphasized that, especially in the extended donor criteria donors, the entire 'procedure' of donor selection/screening and informed consent should be performed by a dedicated team, consisting of nephrologists, transplant surgeons, cardiologists, transplant coordinators, social workers, dietitians, and nursing staff, who are recognized for their expertise in this specific field. In relatively low-volume centers, inherently the experience could be less and therefore we feel that extended criteria donors should be referred to a high-volume center.

Altogether, selecting extended criteria live kidney donors has to be a well-considered multidisciplinary decision, and all options should be explored beforehand, as the use of live kidney donors without comorbidities intuitively will remain preferred. However, with the increasing demand for kidney donors and the subsequent changing tendency regarding contraindications for live kidney donation, the future live kidney donor may not be the same as the donor from the past.

MATERIALS AND METHODS

All aspects of the Cochrane Handbook for Interventional Systematic Reviews were followed, and the study was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[148]

Literature search strategy

Comprehensive searches were carried out in Embase, Medline OvidSP, CENTRAL (the Cochrane Library 2013, issue 10), Web-of-Science, PubMed Publisher and Google Scholar. The search was performed for articles published until November 2013 using search terms specific to each search engine, provided in the Supplementary Data. In addition, 'related citations' in PubMed and cross-referencing were used to search for relevant articles. We focused on the outcome of the live donor nephrectomy and therefore excluded articles regarding deceased kidney donors and outcome in kidney transplant recipients.

Literature screening

Articles were screened by two independent researchers (ARA, JAL) for relevance and possible inclusion. In case of discrepancy, a third author was consulted (FJMFD). After assessing the results of the systematic literature search, articles regarding older donor age, overweight and obesity, hypertension, vascular anomalies or multiplicity, women of childbearing age (nulliparous women), and minors as potential

a

Level	Therapy/prevention, Etiology/harm	Prognosis	Diagnosis	Differential diagnosis/symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations	SR (with homogeneity*) of level 1 diagnostic studies; CDR† with 1b studies from different clinical centers	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of level 1 economic studies
1b	Individual RCT (with narrow confidence interval‡)	Individual inception cohort study with > 80% follow-up; CDR† validated in a single population	Validating** cohort study with good††† reference standards; or CDR† tested within one clinical center	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	All or none case series	Absolute SpPins and SnNouts††	All or none case series	Absolute better-value or worse-value analyses††††
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of level>2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of level>2 economic studies
2b	Individual cohort study (including low quality RCT; e.g. <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; derivation of CDR† or validated on split sample§§§ only	Exploratory**cohort study with good††† reference standards; CDR† after derivation, or validation only on split sample§§§ or databases	Retrospective cohort study or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses.
2c	'Outcomes' research; ecological studies	'Outcomes' research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity*) of case–control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
3b	Individual case–control		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor-quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations
4	Case series (and poor-quality cohort and case-control studies§§	Case series (and poor-quality prognostic cohort studies***)	Case–control study, poor or non-independent reference standard	Case series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research, or 'first principles'	Expert opinion without explicit critical appraisal, or based on physiology, bench research, or 'first principles'	Expert opinion without explicit critical appraisal, or based on physiology, bench research, or 'first principles'	Expert opinion without explicit critical appraisal, or based on physiology, bench research, or 'first principles'	Expert opinion without explicit critical appraisal, or based on economic theory, or 'first principles'

b

a	Consistent level 1 studies
b	Consistent level 2 or 3 studies or extrapolations from level 1 studies
c	Level 4 studies or extrapolations from level 2 or 3 studies
d	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level

FIGURE 3. Oxford Centre for Evidence-based Medicine – Levels of Evidence. (a) Oxford Centre for Evidence-based Medicine Levels of Evidence Scales. (b) Oxford Centre for Evidence-based Medicine Grades of Recommendation.

donors, were selected for further screening. All selected articles were screened for relevance, utility, and reliability. Articles were evaluated using the PICO method.[149] Furthermore, we used the Oxford level of evidence table to grade the literature for each extended criterion (Figure 3a).[150] A grade of recommendation (Figure 3b) is given after each extended criterion is summarized. The aim of grading recommendations is to provide transparency between the underlying evidence and the recommendation given. In addition, the GRADE tool was used to further enlarge the transparency of the quality of the available literature.[151] The GRADE approach defines the quality of a body of evidence by consideration of within-study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTART MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

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Chapter 3

Attitudes among transplant professionals towards shifting paradigms in live kidney donation

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ABSTRACT

Introduction There is a worldwide donor organ shortage, and even though live kidney donation successfully expands the donor pool, it still cannot meet the demand. The transplant community increasingly accepts extended criteria live kidney donors, however great (geographical) differences are present in policies regarding the acceptance of these donors, and guidelines do not offer clarity in this respect. The aim of this survey was to reveal these differences and to get an insight in both center policies as well as personal beliefs of transplant professionals.

Methods An online survey was sent to 1128 European Society for Organ Transplantation (ESOT) members. The questionnaire consisted of two parts; an objective part asking for center policies regarding acceptance of extended criteria live kidney donors, and a subjective part, regarding transplant professionals' personal beliefs in this matter. Questions were included about several extended donor criteria, such as overweight/obesity, age limit, vascular multiplicity, minors as donors and comorbidities like hypertension, impaired fasting glucose, kidney stones, malignancies, and renal cysts. Furthermore, questions about preoperative imaging, multidisciplinary team discussions, and operative techniques were included. Comparisons were made between transplant centers of three regions in Europe (Northwest, Mediterranean and East) and between Europe and other countries worldwide. Results were also categorized to investigate whether center volume is of influence on center policies and personal beliefs.

Results 331 questionnaires (29.3%) were completed by professionals from 55 countries (30 in Europe). Fifty-five percent were transplant surgeons, 35.3% were transplant nephrologists, and the remaining 9.7% were scientists. Significant differences exist between regions in Europe in acceptance of donors with several extended criteria. Median refusal rate for potential live donors is between 10% and 20%. Furthermore, differences are seen regarding preoperative work-up, both in specialists who perform screening as in preoperative imaging. Remarkably, 23.4% of transplant professionals sometimes deviate from their center policy, resulting in more or less comparable personal beliefs regarding extended criteria. Furthermore, if center volume is smaller, transplant professionals are more reluctant in accepting these kinds of donors. Laparoscopic transperitoneal donor nephrectomy is most practiced in Europe as operation technique.

Discussion By performing this survey amongst a large group of transplant professionals in Europe and other countries around the world, we gained insight in both center policies as well as personal opinions regarding acceptance of extended criteria donors. Variety is seen, proving the need for a standardized approach in selection, preferably evidence based. Although short-term outcome of these donors seems to be good, prospectively organized long-term follow-up is warranted to ensure optimal donor safety.

INTRODUCTION

The increased global incidence and prevalence of diabetes, hypertension, obesity, and other risk factors for kidney disease leads to an increased incidence of end-stage renal disease (ESRD).[1] The goldstandard treatment for patients with ESRD is kidney transplantation, but unfortunately, this field is still suffering from the lack of donor organs.[2] Luckily, during the last decades, live kidney donation has proven to successfully expand the donor pool, however, it still cannot meet the demand for donor kidneys.[2] This, together with the excellent results of live donor kidney transplantation, leads to an increase in the acceptance of live donors with so called 'extended donor criteria', i.e., older donors, overweight/obese donors, donor kidneys with vascular multiplicity, donors with comorbidities, women of childbearing age, and even minors as potential donors.[3] In general, live kidney donors are in good health and therefore it is critical that these potential donors do not become patients themselves. Especially in extended criteria donors, careful preoperative screening is of the utmost importance. Since the start of live kidney donation programs, donor assessment and surgical aspects have developed impressively, as well as donor management and follow-up.[4,5] As a result, a shift has occurred in relative and absolute contraindications for live kidney donation, and more extended criteria donors are deemed suitable to donate.[3,6] Unfortunately, the contraindications vary greatly between transplant centers worldwide, and even nationally.[7] Transplant professionals have the responsibility to perform individual risk calculations to ensure donor safety. Therefore, the choice to accept a potential donor becomes a rather subjective issue. We previously published a systematic review to reveal the current opinions of available guidelines regarding extended criteria donors and evidence regarding the outcome of these donors.[3] Current guidelines are not very clear regarding these extended criteria. Furthermore, the level of evidence of the studies that investigated these specific criteria is low, which can be attributed to the fact that outcome of these donors can only be revealed in observational studies. To retrieve more insight in center policies and opinions/attitudes of transplant professionals on this topic, we now performed an online survey amongst European Society of Organ Transplantation (ESOT) members to reveal potential differences between center criteria and personal opinions of eligibility criteria of live kidney donors, both between continents as between the European centers.

METHODS

Study population

The European Society for Organ Transplantation (ESOT) is an umbrella organization under which transplant activities are structured and streamlined in Europe and worldwide. ESOT members are dedicated professional volunteers that represent expert knowledge on donation and transplantation. The organization provides an extensive education programme and her members are involved in generating guidelines in the field of transplantation.

Online survey

An online survey was performed using SurveyMonkey.[8] With ESOT president approval, the questionnaire was sent to all ESOT members who were profiled in the member database as 'surgeon', 'physician' or 'scientists' and/or selected 'kidney' in their profile. On the first page of the survey, participants were obliged to select whether they were either a (transplant) surgeon or a (transplant) nephrologist. All other categories (researcher or other) were then excluded from the rest of the questionnaire. Transplant surgeons were asked whether they perform live donor nephrectomies independently; only if the answer was 'yes', they could continue the survey.

The survey consisted of two parts: a center criteria part, which was presented to both transplant surgeons and nephrologists, and a personal criteria part, which was presented to transplant surgeons for additional specific surgical questions. In total, the survey consisted of 40 questions; 24 center criteria questions and 16 personal criteria questions. Questions were included about several extended donor criteria, such as overweight/obesity, age limit, vascular multiplicity, minors and women of childbearing age as donors, renal anatomy and comorbidities like hypertension, impaired fasting glucose, and kidney stones. In the personal criteria part, a five-point Likert scale was presented, rating from 1 'very unlikely' to 5 'very likely'. Ratings of 3 were considered 'neutral'. Since it is of great importance that a potential donor is carefully assessed regarding anatomy and function of the kidney(s), we have included several questions about preoperative radiological imaging and functional testing of the kidneys. The questionnaire is included as supplemental data. Results were divided into the answers of different European centers (Northwest, Mediterranean and East (for exact division, see supplemental data), to compare policies and attitudes within Europe. Also, data is presented to reveal potential differences between continents in the world (supplemental data). Furthermore, in order to investigate the hypothesis that center policies or personal feelings might differ if analyzed by center volume (number of live donor nephrectomies (LDNs) performed annually), we divided results in the following groups: (0-25 LDNs per year; 26-50, 51-100, 100+) (supplemental data).

Data collection

The initial invitation to participate with the survey was sent on the 14th of August 2014. Two reminders were sent, each with one month in between.

Statistical analysis

All analyses were conducted using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp. Released 2012. Armonk, NY: IBM Corp.). Categorical variables were compared using the Chi-square test and continuous variables were compared with the Mann-Whitney *U* test or the Kruskal-Wallis test. A *P*-value less than 0.05 was considered statistically significant.

RESULTS

The online survey was sent to 1128 ESOT members of whom 331 (29.3%) completed the online survey. 182 respondents were (transplant) surgeons, 117 were (transplant) nephrologists, and 32 had another professional function. Of the 182 surgeons, 101 performed live donor nephrectomies independently. Three surgeons did not mention whether they performed the operation independently and were excluded from the personal criteria analysis. The remaining 78 surgeons that did not perform nephrectomies independently were excluded from the survey, as well as the 32 transplant professionals who were not a surgeon or nephrologist. After excluding the aforementioned participants, 221 questionnaires were included for analyses. A flow-chart of the process is depicted in Figure 1. It has to be noticed that it could be that several respondents work in the same center, and thus, this may introduce some bias. Therefore, in the results of the center criteria 'x% of the transplant centers' should be read as 'x% of the respondents filled out that their center...'.

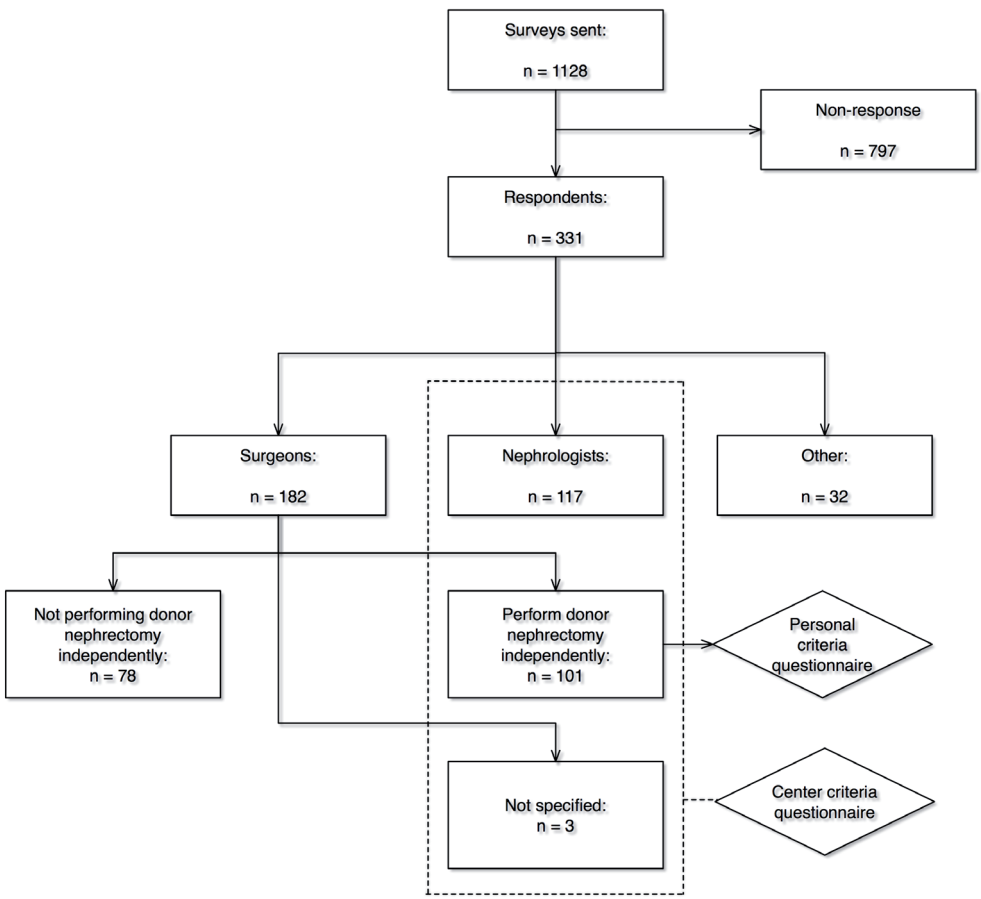

FIGURE 1. Flowchart of the inclusion and exclusion of the questionnaire respondents.

Center criteria

An overview of all the center criteria questions is shown in Table 1. The 187 respondents from Europe were divided as follows: 113 from northwestern countries, 55 from Mediterranean countries, and 19 from eastern countries. The mean number of live donor renal transplantations performed amongst the centers of ESOT members (European and non-European members) was 40.9 ± 37.5 / year. For Europe, this number was more or less the same. Between regions in Europe, there was a significant difference ($P<0.001$), the highest number of live donor renal transplantations was in the northwestern transplant centers (55 ± 40.5). The mean number of transplantations from deceased donors in ESOT member centers was 68.9 per year. Respondents in Eastern Europe perform the most transplantations, and Mediterranean countries the least, with a significant difference between regions ($P= 0.03$). Furthermore, significant differences were seen when answers were divided based on center volumes (supplemental data).

Overweight and obesity 99.5% of the respondents centers accept donors with overweight (>25 BMI <30), 69.5% accept obese donors (BMI 30-35), morbidly obese donors are considered in 16.2% of the centers, and only 5.1% accept donors with a BMI higher than 40. The question was raised whether transplant centers in Europe differ in accepting possible donors with higher BMIs. No significant differences were seen between regions.

Minors, women and impaired fasting glucose 3.6% accept minors (age <18 years) as donors and 82.2% women of childbearing age. Donors with an impaired fasting glucose (defined as fasting plasma glucose of 100 to 125 mg/dl) are considered by 42.9% of the respondents' centers.

Hypertension Donors with hypertension are accepted in 5.8% of the respondents' centers, even if not controlled with antihypertensive medication; 47.6%, 32.8% and 1.6% of the centers accept these donors if the hypertension is controlled with 1, 2, or more than 2 agents, respectively. 12.2% of the centers decline donors with hypertension, regardless if well controlled with medication, which is interesting, as current guidelines report that donors with hypertension controlled with up to two agents can be safely included for donation.[9] A significant difference exists between regions in Europe ($P=0.04$).

Older donors 57.1% of the respondents' centers have no upper age limit for live kidney donors. 1.1% of the centers have an undefined age limit. Again, a significant difference is seen between centers in Europe ($P<0.01$).

Vascular multiplicity Arterial multiplicity and venous multiplicity are not considered a contraindication in 93.1% and 91.0% of the respondents' centers, respectively. In Europe, it seems that Mediterranean and Eastern centers have more strict policies regarding vascular multiplicity, with significant differences both in arterial as in venous multiplicity.

TABLE 1. Overview of center criteria questions.

Mean (SD)	**Total (n=221)**	**Europe (n=187)**	**Northwest (n=113)**	**Mediterranean (n=55)**	**East (n=19)**	***P*-value Overall**
Kidney Tx from a live donor (numbers/region/year)	40.9 (37.5)	40.9 (38.3)	55 (40.5)	18.4 (21.3)	22.6 (21)	**<0.001**
Kidney Tx from a deceased donor (numbers/region/year)	68.9 (48.8)	80 (47.5)	80.2 (47.8)	62.5 (38.0)	80.6 (65.9)	**0.031**
Does your center accept donors with the following BMI categories?						
Overweight	99.5%	99.4%	100%	100%	93.8%	**0.009**
Obesity	69.5%	69.5%	71.3%	64.0%	75.0%	0.579
Morbid Obesity	16.2%	15%	17.8%	12.0%	6.3%	0.378
Morbid Obesity (Class II)	5.1%	4.2%	5.0%	4.0%	0%	0.654
Does your center accept minors (<18 years) as donors?						
Yes	3.6%	3.6%	5.0%	2.0%	0%	0.472
Does your center accept women of childbearing age as donors?						
Yes	82.2%	82%	85.1%	80.0%	68.8%	0.257
Does your center accept donors with impaired fasting glucose?						
Yes	42.9%	41.5%	40.6%	44.9%	35.7%	0.796
Does your center accept donors with hypertension?						
No	12.2%	10.1%	10.4%	4.1%	28.6%	**0.039**
If controlled with 1 agent	47.6%	47.2%	39.6%	65.3%	35.7%	
If controlled with 2 agents	32.8%	35.2%	40.6%	24.5%	35.7%	
If controlled with > 2 agents	1.6%	1.3%	2.1%	0%	0%	
Yes	5.8%	6.3%	7.3%	6.1%	0%	
Does your center have an upper age limit for live kidney donors?						
Yes	1.1%	0.6%	1.0%	0%	0%	**0.003**
Yes, max 60	5.3%	1.9%	1.0%	2.0%	7.1%	
Yes, max 65	10.1%	8.2%	4.2%	18.4%	0%	
Yes, max 70	10.6%	10.1%	3.1%	18.4%	28.6%	
Yes, max 75	10.1%	6.9%	7.3%	6.1%	7.1%	
Yes, max 80	5.3%	5.0%	5.2%	6.1%	0%	
No age limit	57.1%	67.3%	78.1%	49.0%	57.1%	
Does your center accept donors with more than 1 renal artery?						
No	6.9%	8.2%	2.1%	14.3%	28.6%	**<0.001**
Yes, max 2 arteries	40.7%	40.3%	31.3%	55.1%	50.0%	
Yes, max 3 arteries	21.7%	20.8%	28.1%	12.2%	0%	
Yes, max 4 arteries	3.2%	2.5%	3.1%	2.0%	0%	
Yes, no maximum	27.5%	28.3%	35.4%	16.3%	21.4%	

TABLE 1. (Continued)

Mean (SD)

	Total (n=221)	Europe (n=187)	Northwest (n=113)	Mediterranean (n=55)	East (n=19)	*P*-value Overall
Does your center accept donors with more than 1 renal vein?						
No	9%	10.7%	5.2%	16.3%	28.6%	**0.010**
Yes, max 2 veins	38.1%	35.8%	29.2%	46.9%	42.9%	
Yes, max 3 veins	20.1%	18.2%	25.0%	8.2%	7.1%	
Yes, max 4 veins	0.5%	0.6%	1.0%	0%	0%	
Yes, no maximum	32.3%	34.6%	39.6%	28.6%	21.4%	
Does your center accept donors with kidney stones?						
No	26.9%	26.9%	21.3%	31.3%	50.0%	0.163
Yes, but only if the remaining kidney is free	54.3%	53.8%	58.5%	52.1%	28.6%	
Yes	18.8%	19.2%	20.2%	16.7%	21.4%	
Does your center accept donors with one or more kidney stones in the contralateral kidney?						
Yes	14%	12.2%	11.7%	12.5%	14.3%	0.959
Does our center accept kidneys with a renal malignancy smaller than 3 cm?						
Yes	21%	22.4%	30.9%	12.5%	0%	**0.005**
Does your center accept donors with renal cysts?						
Yes, max Bosniak I	33.9%	32.1%	42.5%	52.7%	36.8%	0.345
Yes, max Bosniak II	39.8%	41.2%	46.9%	40.0%	36.8%	0.566
Yes, max Bosniak IIF	10%	9.6%	9.7%	9.1%	10.5%	0.982
Yes, max Bosniak III	0.5%	0.5%	0%	1.8%	0%	0.299
Yes, max Bosniak IV	0%	0%	0%	0%	0%	-
Which specialist(s) does a donor meet during a regular screening in your center?						
(Transplant) surgeon	70.6%	70.1%	69.9%	78.2%	47.4%	**0.041**
(Transplant) nephrologist	82.8%	81.8%	82.3%	83.6%	73.7%	0.611
Anesthesiologist	46.2%	48.1%	46.0%	58.2%	31.6%	0.105
Social worker	26.7%	22.5%	30.1%	12.7%	5.3%	**0.007**
Nurse practitioner	41.6%	42.2%	52.2%	32.7%	10.5%	**0.001**
Psychologist/Psychiatrist	42.5%	41.7%	36.3%	58.2%	26.3%	**0.009**
Other	15.8%	15.5%	18.6%	12.7%	5.3%	0.264
Is every donor discussed in a multidisciplinary team?						
Yes	90.3%	90.4%	89.4%	89.6%	100%	0.441
Which specialist(s) are part of the multidisciplinary team of your center?						
(Transplant) surgeon	73.8%	72.7%	71.7%	74.5%	73.7%	0.922
(Transplant) nephrologist	74.2%	73.3%	71.7%	76.4%	73.7%	0.812
Anesthesiologist	38.5%	40.1%	32.7%	50.9%	52.6%	**0.039**
Social worker	20.4%	13.4%	15.9%	10.9%	5.3%	0.367
Nurse practitioner	51.6%	48.1%	56.6%	38.2%	26.3%	**0.011**
Psychologist/Psychiatrist	38.0%	36.9%	26.5%	56.4%	42.1%	**0.001**
Other	21.3%	19.3%	21.2%	16.4%	15.8%	0.695

TABLE 1. (Continued)

Mean (SD)

	Total (n=221)	Europe (n=187)	Northwest (n=113)	Mediterranean (n=55)	East (n=19)	*P*-value Overall
Does your center perform standard pre-operative imaging during the screening of donors?						
Yes	100%	100%	100%	100%	100%	-
What modalities of pre-operative imaging are used in your center?						
MRI/MRA	15.4%	17.6%	23.0%	9.1%	10.5%	0.059
CT/CTA	73.3%	70.6%	67.3%	78.2%	68.4%	0.337
Invasive angiography	4.1%	2.7%	2.7%	1.8%	5.3%	0.725
Ultrasound	46.6%	45.5%	38.9%	50.9%	68.4%	**0.036**
Other	5.9%	5.3%	8.0%	1.8%	0%	0.138
Do you perform standard radioisotope renography as part of the live donor screening process?						
Yes	65.4%	67.7%	60.2%	79.2%	78.6%	**0.049**
What kind of functional screening do the donors in your center undergo?						
MAG-3 scan	35.3%	37.4%	44.2%	23.6%	36.8%	**0.035**
DTPA-scan	28.1%	24.6%	14.2%	45.5%	26.3%	**<0.001**
DMSA-scan	19.0%	18.2%	19.5%	18.2%	10.5%	0.646
Other	13.6%	13.9%	19.5%	5.5%	5.3%	**0.025**
What kind of surgical techniques are practiced in your center?						
Open (lumbotomy)	17.6%	15.5%	8.8%	23.6%	31.6%	**0.006**
Open (mini-incision)	25.8%	26.7%	27.4%	23.6%	31.6%	0.769
Laparoscopic transperitoneal	32.1%	29.9%	31.0%	32.7%	15.8%	0.354
HALS	31.2%	29.9%	31.9%	27.3%	26.3%	0.777
Retroperitoneoscopic – no hand-assistance	5.4%	5.3%	6.2%	5.5%	0%	0.539
HARP	15.8%	17.1%	25.7%	3.6%	5.3%	**0.001**
Robot-assisted laparoscopic transperitoneal	8.6%	10.2%	10.6%	12.7%	0%	0.276
Other	2.3%	1.1%	1.8%	0%	0%	0.516

SD: standard deviation, Tx: transplantation, BMI: Body Mass Index, MAG-3 scan: Mercaptoacetyltriglycine-scan, DTPA-scan: Diethylene Triamine Pentacaetic Acid-scan, DMSA-scan: dimercaptosuccinic acid-scan, HALS: Hand-assisted laparoscopic transperitoneal, HARP: Hand-assisted retreoperitoneoscopic laparoscopic.

Cysts 33.9% of the respondents' centers accept donors with renal cysts only when the Bosniak classification is I. Kidney donors with a Bosniak II cyst are accepted by 39.8%. For Bosniak IIF (malignancy risk 5 -10%), 6.6% of the centers are willing to accept such a donor.

Kidney stones 26.9% accept no donors with kidney stones, however 54.3% accept a kidney with a stone if the contralateral (remaining) kidney is free of stones. Only 14% accept a donor if the contralateral kidney contains one or more stones.

Renal malignancies Renal malignancies smaller than 3 cm are accepted by 21% of the respondents' centers. Northwestern centers have the highest acceptance rate of these donors, versus 0% of the Eastern centers ($P<0.01$).

Multidisciplinary teams In 90.3% of the respondents' transplant centers, every donor is discussed in a multidisciplinary team. We wondered if the composition of the specialists that a potential living kidney donor meets in context of a regular screening differs between regions. The exact percentages can be found in Table 1. Interestingly, there are significant differences in specialists that screen donors between European regions. Thirty-five respondents filled out that their donors are also screened or seen by other professionals than the 'standard' list as part of regular screening, amongst which are ward nurses, transplant coordinators, urologists, cardiologists, independent donor advocates, kidney transplant recipients, health educators, members of an ethical committee, and sometimes even an endocrinologist or gynecologist. Forty-seven participants responded that also other professionals are part of the multidisciplinary team, amongst which transplant coordinators, radiologists, immunologists, geneticists, cardiologists, and urologists. Regarding the composition of this team, also significant differences are seen between regions in Europe. Of the centers that do not discuss every donor in a multidisciplinary team (9.6%), only the (transplant) surgeon or nephrologist decides on the final acceptance of the donor.

Imaging and functional scanning All respondents' transplant centers perform standard imaging during the screening process. Most of the centers (73.3%) use CT or CTA as imaging modality to assess the renal anatomy. Following CT, ultrasound is used in 46.6% of the centers, however not as the only modality (mostly in combination with CT). Only in the use of ultrasound, a significant difference was found between European centers, where Northwestern centers use ultrasound least frequently, and centers in Eastern countries use it the most. The respondents that filled out that other types of imaging are used misinterpreted functional screening methods like radioisotope renography with imaging techniques.

Standard radioisotope renography is performed in 65.4% of the respondents' centers, of which a MAG3-scan is performed in 35.3% of these centers. In Mediterranean centers, radioisotope renography is used the most, compared with other European regions ($P=0.05$). There are some differences in the use of the several available modalities between regions. Reasons for not performing standard radioisotope renography are that there is no need to perform it (because the use of imaging modalities seem sufficient), or only if there is a significant size discrepancy between the two kidneys, or other reasons to suspect the relative functional contribution of each kidney to total renal function is different. Other functional screening modalities mentioned were EDTA- or iohexol clearance calculations.

Surgical techniques of live donor nephrectomy Although laparoscopic donor nephrectomy[10] is considered as gold standard in most of the transplant centers, still several other (or newly developed) techniques are practiced. Despite the outcome of some high-quality randomized controlled trials and meta-

analyses,[11-13] the open technique via a lumbotomy or mini-incision[14] is used in 17.6% and 25.8% of the centers, respectively. The open technique is mostly performed in Eastern centers (31.6%) and the least in northwestern centers (8.8%). 31.2% perform the hand-assisted laparoscopic technique,[15] and 15.8% the hand-assisted retroperitoneoscopic technique.[16] Pure retroperitoneoscopic approaches,[17] and robot-assisted laparoscopic donor nephrectomy[18] are practiced in 5.4% and 8.6% of the respondents' centers, respectively. Amongst the respondents that filled out 'other technique(s)', the open mini anterior extraperitoneal technique was mentioned.

Personal criteria

In total, 101 of the 182 surgeons that performed donor nephrectomies independently, filled out the personal criteria questionnaire, consisting of 85 surgeons working in European centers amongst which were 64 surgeons from Northwestern centers, 17 from Mediterranean, and 4 from Eastern centers. Medians and ranges of the five-point Likert scale are presented in Table 2. Furthermore, regarding several outcome measures, significant differences were seen between continents and also when answers were divided based on center volumes (supplemental data).

Overweight and obesity Surgeons from all regions would likely perform a donor nephrectomy in overweight (BMI 25-30) donors (5 (2-5)). The likelihood of accepting the potential donor decreases with increasing BMI class, with a median of 3, 2, and 1, respectively, without statistical differences between European centers.

Minors as donors Regarding minors as potential donors, surgeons are mostly consistent, and are not likely to consider a minor as potential donor.

Women of childbearing age Women of childbearing age are likely to be accepted as donor, with no differences between centers.

Impaired fasting glucose Regarding donors with impaired fasting glucose, most transplant professionals are more reluctant, stating that it is unlikely that they would accept such a donor.

Older age The median age limit for potential donors varies between regions, however not significantly different. In the ESOT-centers, the upper age limit ranges from 60 to 'no age limit'. This is in line with the finding that two-third of the centers have no age limit for potential donors.

Hypertension There seems to be consistency between all groups regarding the acceptance likelihood of donors with hypertension. All groups show that they would rather accept a donor with hypertension controlled with 1 agent than a hypertensive donor without agents.

Vascular multiplicity In all regions, surgeons replied that they consider the arterial renal anatomy to be more important than the venous anatomy, except for the Eastern centers, where the renal and the venous anatomy are considered equally important. Regarding vascular multiplicity, as expected, surgeons are less likely to accept a donor with more arteries or veins, and this is not significantly different between regions regarding the arterial anatomy. As for the venous anatomy however, there is some difference between regions in selection of donors with two or three renal veins (P=0.02 and P<0.05)

Kidney stones Nearly all regions have a neutral or positive opinion about donating a kidney with stones (median of 3). However, it is less likely that surgeons would perform a donor nephrectomy while the remaining kidney contains one or more stones (median of 2).

Preferred surgical techniques of donor nephrectomies As presented in the center-criteria part of the survey, still 17% of the centers perform the lumbotomy for graft retrieval, and about a quarter uses the mini-open technique. These techniques seem to be less preferred, showing that the laparoscopic transperitoneal is the most favorite technique, closely followed by the hand-assisted technique. The relatively newer techniques are significantly less preferred in Eastern centers, in contrast to the open lumbotomy technique, which is preferred in 50% of the Eastern centers (P<0.001). This could be attributed by the fact that these centers might not have access to these new techniques. 26.3% of the respondents chose more than one technique as preferable.

Refusal of potential living kidney donors In total, between 20% and 30% of the participants sometimes refuse a possible live kidney donor. There is no significant difference between continents. The top three reasons for refusal were: hypertension (12.1%), glucose levels (diabetes) (10.5%), and renal (dys)function (9.7%). Other reasons for refusal of a potential donor were: anatomy, overweight/obesity, or other comorbidities. Participants were also asked if they maintain other criteria, which were not previously mentioned to refuse a donor. Several criteria were mentioned; psychological reasons, ethical uncertainty (commercial or coercion), or uncertainty of the motivation of the possible donor. No differences were seen between centers in Europe.

Deviation from center policy Interestingly, 23.7% of the surgeons (sometimes) deviate from their center policy regarding extended criteria. Between regions in Europe, there seems to be no significant difference, although none of the surgeons in Eastern countries deviate from their center policy. Body weight was the criterion that was most frequently mentioned as reason to deviate from center policy (77.3%). No differences exist between centers in Europe. Interestingly, however, a significant difference was seen between continents regarding 'older age' as reason to deviate from the center policy (P<0.01, supplemental data). American transplant surgeons are much more likely to deviate from their center policy regarding donor age than European centers.

TABLE 2. Overview of personal criteria questions using a 5-point Likert scale; 1 is considered 'very unlikely' and 5 'very likely'.

Median + ranges	Total (n=101)	Europe (n=85)	Northwest (n=64)	Mediterranean (n=17)	East (n=4)	*P*-value
How likely is it that you would personally perform a live donor nephrectomy in a donor who is:						
Overweight (25-30)	5 (2-5)	5 (2-5)	5 (3-5)	4 (2-5)	5 (4-5)	**0.002**
Obese (30-35)	3 (1-5)	3 (1-5)	4 (1-5)	3 (1-5)	4 (3-5)	0.062
Morbidly obese (35-40)	2 (1-5)	2 (1-5)	2 (1-5)	1 (1-4)	2 (1-2)	0.158
Morbidly obese (40+)	1 (1-5)	1 (1-5)	1 (1-5)	1 (1-3)	1 (1-1)	0.166
Upper age limit for LKD	60 (60-no age limit)	No age limit (no age limit-other)	No age limit (no age limit-other)	70 (no age limit-other)	70 (no age limit-other)	0.112
Minors as donors	1 (1-5)	1 (1-5)	1 (1-5)	1 (1-4)	1 (1-1)	0.153
Women of childbearing age	4 (1-5)	4 (1-5)	4 (1-5)	3 (2-5)	4 (2-4)	0.254
Impaired fasting glucose	2 (1-5)	2 (1-5)	2 (1 -5)	2 (2-4)	2 (1-2)	0336
How likely is it that you would personally accept a donor with hypertension with the following conditions:						
Without agents	3 (1-5)	3 (1-5)	3 (1-5)	3 (1-5)	4 (2-5)	0.471
If well controlled with 1 agent	4 (1-5)	4 (1-5)	4 (1-5)	4 (2-5)	4 (1-5)	0.257
If well controlled with 2agents	2 (1-5)	2 (1-5)	2 (1-5)	2 (1-4)	3 (1-4)	0.739
If well controlled with >2agents	1 (1-5)	1 (1-5)	1 (1-5)	1 (1-2)	1 (1-2)	0.816
What is in your opinion more important, the arterial or the venous anatomy?						
	Artery	Artery	Artery	Artery	Equally important	0.636
How likely is it that you would personally accept a donor with the following number of renal arteries?						
1 renal artery	5 (3-5)	5 (3-5)	5 (5-5)	5 (4-5)	5 (5-5)	0.135
2 renal arteries	5 (2-5)	5 (2-5)	5 (2-5)	4 (2-5)	5 (4-5)	**0.001**
3 renal arteries	3 (1-5)	3 (1-5)	3 (1-5)	2 (1-4)	2 (2-4)	0.109
4 renal arteries	2 (1-5)	2 (1-5)	2 (1-5)	1 (1-4)	1 (1-2)	0.236
>4 renal arteries	1 (1-5)	1 (1-5)	1 (1-5)	1 (1-3)	1 (1-2)	0.735
How likely is it that you would personally accept a donor with the following number of renal veins?						
1 renal vein	5 (3-5)	5 (3-5)	5 (4-5)	5 (4-5)	5 (5-5)	0.557
2 renal veins	5 (1-5)	5 (1-5)	5 (2-5)	5 (1-5)	5 (4-5)	**0.018**
3 renal veins	4 (1-5)	4 (1-5)	4 (1-5)	4 (1-5)	2 (1-3)	**0.049**
4 renal veins	2 (1-5)	2 (1-5)	2 (1-5)	2 (1-4)	1 (1-3)	0.299
>4 renal veins	2 (1-5)	2 (1-5)	2 (1-5)	2 (1-4)	1 (1-3)	0.867
How likely is it that you would personally accept a kidney with stones for donation?						
Kidney with stones for donation	3 (1-5)	3 (1-5)	4 (1-5)	3 (1-4)	2 (1-5)	0.179
Stone(s) in contralateral kidney	2 (1-5)	2 (1-5)	2 (1-5)	2 (1-3)	2 (1-2)	0.281

TABLE 2. (Continued)

Median + ranges	Total (n=101)	Europe (n=85)	Northwest (n=64)	Mediterranean (n=17)	East (n=4)	*P*-value
Which technique(s) do you <u>preferably</u> use for live donor nephrectomy?						
Open lumbotomy	6.9%	5.9%	3.1%	5.9%	50.0%	**0.001**
Open (mini-incision)	19.8%	20%	17.2%	29.4%	0%	0.319
Laparoscopic transperitoneal	36.6%	32.9%	34.4%	35.3%	0%	0.356
HALS	31.7%	31.8%	31.3%	35.3%	25.0%	0.909
Retroperitoneoscopic, no hand-assistance	5.9%	4.7%	6.3%	0%	0%	0.502
HARP	19.8%	21.2%	28.1%	0%	0%	**0.024**
Robot-assisted laparoscopic transperitoneal	4.0%	4.7%	1.6%	17.6%	0%	**0.019**
Other	3.0%	2.4%	3.1%	0%	0%	0.715
What is your percentage of refusal for potential live kidney donors?						
	20-30% (0% – 60%)	10-20% (0% – 60%)	20-30% (0% - other)	20-30% (0% – 60%)	20-30% (10% - other)	0.747
Do you sometimes deviate from your center policy?						
Yes	23.7%	23.4%	27.6%	13.3%	0%	0.315
Regarding which donor characteristic do you deviate?						
Weight	77.3%	72.2%	18.8%	5.9%	-	0.199
Blood pressure	36.4%	27.8%	7.8%	0%	-	0.234
Older age	31.8%	16.7%	3.1%	5.9%	-	0.593
Younger age	4.5%	5.6%	1.6%	0%	-	0.604
Women of childbearing age	13.6%	11.1%	3.1%	0%	-	0.460
Impaired fasting glucose	36.4%	33.3%	7.8%	5.9%	-	0.787
Vascular multiplicity	27.3%	27.8%	7.8%	0%	-	0.234

SD: standard deviation, Tx: transplantation, BMI: Body Mass Index, MAG-3 scan: Mercaptoacetyltriglycine-scan, DTPA-scan: Diethylene Triamine Pentacaetic Acid-scan, DMSA-scan: dimercaptosuccinic acid-scan, HALS: Hand-assisted laparoscopic transperitoneal, HARP: Hand-assisted retreoperitoneoscopic laparoscopic.

DISCUSSION

This study describes the current attitudes of transplant professionals regarding extended donor criteria in live kidney donation. Although the response percentage was 29.3%, we received 331 responses, which can be considered as a high number. Furthermore, due to the nature of ESOT membership, our questionnaire was sent to professionals in several continents, allowing for more insight in possible geographical differences.

Since extended donor criteria in live kidney donation have become clinically important, it is crucial to understand current attitudes of transplant professionals. Whether or not it is truly safe for extended criteria donors to donate a kidney will be determined largely by long-term follow-up data. In general,

these long-term data of living kidney donors are not yet available. Although several studies have been published regarding 'medium'-term outcome, the longest follow-up data available is with a follow-up period of around thirty years.[19] Most studies report excellent outcome after live donor nephrectomy in short-term follow-up,[5,19-21] however recent studies are more careful in stating that living donors have excellent outcome.[22,23] As the World Health Organization states that, 'Live donations are acceptable when the donor's informed and voluntary consent is obtained, when professional care of donors is ensured and follow-up is well organized, and when selection criteria for donors are scrupulously applied and monitored',[24] it is important that transplant professionals give accurate information regarding possible complications. Unfortunately, there is no worldwide consensus regarding the informed consent procedure.[25] Especially in the case of extended criteria donors, long-term follow-up data is lacking, as these donors have been increasingly accepted in the last decade. We know that donors with overweight/obesity,[26] and donors with vascular multiplicity have good short-term outcome.[27-29] However, regarding other extended criteria, there is still a lot of uncertainty.

In the center criteria part of the questionnaire we have tried to give an overview regarding the current policies in transplant centers where ESOT members work and made a distinction between several regions within Europe. Acceptance of donors with overweight or obesity is fairly comparable. Some centers accept minors as potential donors, which is an interesting phenomenon, as current guidelines state that minors should only be considered as potential donors if no other options exist, mostly in case of identical twins. It could be that these centers have performed such donations and transplantations; however, we do not have this specific data. There seems to be no reluctance in accepting a woman of childbearing age for kidney donation, which is in line with the Amsterdam Forum criteria, stating that donor nephrectomy is not detrimental to the prenatal course or outcome of future pregnancies.[9] However, recent literature recommends a more careful approach regarding this group of potential donors.[30] Regarding impaired fasting glucose in a potential donor, about half of the centers have no objection, which is in contrast with guidelines (individuals with a history of diabetes or fasting blood glucose greater than or equal to 126 mg/dl (7.0 mmol/l) on at least two occasions (or 2 h glucose with OGTT greater than or equal to 200 mg/ dl (11.1 mmol/l) should not donate).[9] Remarkably, 5.8% of the centers consider a donor with hypertension that is uncontrolled, and even 6.3% of European centers accepts these donors. This is an interesting finding, as guidelines are more or less unanimous; uncontrolled hypertension should be considered as a contraindication for donation.[9,31]

We know from previous studies that older donors have excellent outcome,[32,33] luckily, more than half of the centers have no age limit for the donors. However, there are differences between regions in Europe. In America there seems to be a stronger policy regarding donor age (supplemental data). Several reasons could attribute to this policy. One of the main questions is whether a kidney from a 70-year old will last as long as that from a 50-year old donor. Furthermore, many guidelines have not included statements regarding older age.[9,34,35] The British guidelines however state that older age is not an absolute contraindication for donation, but that the medical work-up of older donors must be particularly rigorous to ensure suitability. They also mention that the older donor may have a greater

risk of developing perioperative complications.[31] However, Klop *et al.*[36] showed that older donors have excellent outcome, and that their cosmesis scores after donor nephrectomy are higher than those of younger donors. Ahmadi *et al.*[3] recently performed a systematic review, combining all available evidence to date, stating that older age does not seem to have a negative impact on the outcome after donor nephrectomy and that it is not necessarily actual age itself, but renal function, the presence of other comorbidities, and overall health that will determine whether an older live kidney donor should be included.

More than a quarter of the centers have no maximum for vascular multiplicity, however, geographical differences exist. The Eastern countries in Europe as well as American centers seem to be more reluctant. The Amsterdam Forum guidelines have not included vascular multiplicity, in contrast to the British guidelines, which state that the presence of multiple renal arteries is no contraindication for donation. As we know that about a quarter of the general population has vascular multiplicity,[37,38] we lose a considerable number of potential donors if these are excluded. Previous studies have shown that both donors as recipients from kidneys with vascular multiplicity have excellent outcome, at least with arterial multiplicity up to three renal arteries.[3] The questions about cysts, kidney stones, and renal malignancies in donor kidneys give no striking results, although Eastern transplant centers do not accept kidneys with renal malignancies. Regarding kidney stones, the guidelines state that an asymptomatic potential donor with a current (or a history of) single stone can be safely selected for donation, but such potential kidney donors should be screened for metabolic stone forming abnormalities (e.g. hypercalcuria, hyperuricemia, hyperoxaluria, hyperuricosuria, hypocitraturia, cystinuria, and metabolic acidosis).[9,31] However, 27% of the centers decline a donor with stones, even if the contralateral kidney is free of stones.

Remarkably, in 30% of the centers, transplant surgeons do not have an outpatient surgical screening, however, over 90% of the centers discusses every donor in a multidisciplinary team. Some significant differences are seen between regions in Europe.

In all centers, donors are preoperatively imaged to assess renal anatomy. CT(A) is mostly used, and seems to be the gold standard worldwide. Available studies show that CT(A) is more accurate than, or at least as accurate as MRA for assessing renal anatomy in live kidney donors.[39,40] Ultrasound is also often used, significantly more in Eastern countries than other centers in Europe. Regarding operative techniques, laparoscopic transperitoneal donor nephrectomy is the most used technique, although the open methods are still practiced in around twenty percent of the transplant centers. The latest developments in this field (LESS donor nephrectomy and NOTES[41,42]) were not mentioned amongst 'other', which is not surprising as these techniques are relatively new.

Almost no differences are seen between the personal criteria and the center criteria part of the questionnaire. Interestingly, European surgeons seem to be more reluctant in accepting women of childbearing age than American surgeons (supplemental data). Little literature is available regarding outcome in this group, with varying results.[43,44] A recent publication by Garg *et al.*[30] however, reports a higher incidence of gestational hypertension and preeclampsia in this group of donors. Another important issue is the percentage of donor refusal. Overall, around 20-30% of the donors are excluded,

for reasons previously mentioned, although we are not sure exactly when in the screening process these donors are declined. Renal dysfunction is an obvious reason to exclude a donor, however, hypertension and impaired fasting glucose are comorbidities, which can be treated with life-style advices or medication. These candidates might be eligible for donation if their comorbidities were controlled. On the other hand, it is reassuring that transplant professionals seem to be extremely careful in including these types of donors, especially since we are not optimally informed on their long-term follow-up.

One of the most daring questions was whether a respondent sometimes deviates from center policy. A quarter of the surgeons sometimes deviate, mostly if the possible donor is overweight or obese. This could be explained by the fact that the BMI does not take the fat distribution into account, and that an obese donor might be perfectly suitable in terms of surgical difficulty. American surgeons seem to be more inclined to overrule their center policy regarding the age limit of a possible donor. This significant difference can be attributed to the fact that American centers hold stricter age limit policies.

Limitations

The response percentage of this survey was 29.3%, which could be considered low. However, we sent the questionnaires to all ESOT members who were enlisted as 'surgeon', 'physician' and/or 'scientists', and selected "kidney" as their expertise. Logically, several ESOT members were enlisted as such, however, were not a transplant surgeon or nephrologist. We assume that the response percentage is lower, because of the fact that some of the invitees already knew they did not meet the inclusion criteria. Furthermore, not all transplant centers around the world have a live kidney donation program, and are therefore less likely to respond. Secondly, the majority of the responses came from European professionals, due to the fact that the ESOT is a European society and inherently, most members come from Europe. This leads to a suboptimal statistical analysis because of the low response from other continents. However, we still felt that it would give a good insight in continental differences regarding attitudes of extended criteria live kidney donation.

Concluding, in this era of organ shortage, extended criteria donors are increasingly considered as candidates for live kidney donation. There is still great discrepancy between available guidelines, literature and as we now know, attitudes of transplant professionals regarding extended criteria donors. Guidelines are very superficial regarding some extended criteria, over the last years however, more and more literature has become available, showing good short-term outcome of extended criteria donors. Although we should bear in mind that long-term outcome of these donors still has to be unraveled, it is clear that (based on the results of this survey), transplant professionals are prepared to accept these donors. By performing this survey, we aimed to give the transplant community more insight in their policies and attitudes, hopefully leading to an eventual consensus regarding extended criteria donors, and thereby enlarging the donor pool.

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Chapter 4

The need for a standardized informed consent procedure in live donor nephrectomy: A systematic review

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ABSTRACT

Background Informed consent in live donor nephrectomy is a topic of great interest. Safety and transparency are key items increasingly getting more attention from media and healthcare inspection. Because live donors are not patients, but healthy individuals undergoing elective interventions, they justly insist on optimal conditions and guaranteed safety. Although transplant professionals agree that consent should be voluntary, free of coercion, and fully informed, there is no consensus on which information should be provided, and how the donors' comprehension should be ascertained.

Methods Comprehensive searches were conducted in Embase, Medline OvidSP, Web-of-Science, PubMed, CENTRAL (The Cochrane Library 2014, issue 1) and Google Scholar, evaluating the informed consent procedure for live kidney donation. The methodology was in accordance with the Cochrane Handbook for Interventional Systematic Reviews and written based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Results The initial search yielded 1,009 hits from which 21 articles fell within the scope of this study. Procedures vary greatly between centers, and transplant professionals vary in the information they disclose. Although research has demonstrated that donors often make their decision based on moral reasoning rather than balancing risks and benefits, providing them with accurate, uniform information remains crucial because donors report feeling misinformed about or unprepared for donation. Although a standardized procedure may not provide the ultimate solution, it is vital to minimize differences in live donor education between transplant centers.

Conclusion There is a definite need for a guideline on how to provide information and obtain informed consent from live kidney donors to assist the transplant community in optimally preparing potential donors.

With low complication and mortality rates, live donor nephrectomy is a safe, low-risk surgical procedure. In contrast to patients, living donors are (generally) healthy individuals in whom a vital organ is removed for the benefit of others. It is of the utmost importance that any patient is correctly informed about the specific details, risks, and alternatives of a procedure, but the unique character of the live donor nephrectomy may warrant an extra vigilant approach to the informed consent process. Relevance further increases because extended criteria donors (e.g., overweight/obese donors, older donors, donors with hypertension, and/or vascular multiplicity/anomalies) are increasingly being accepted. These individuals could be more prone to complications, and potential donors must be well aware of the risks involved with their upcoming procedure.[1]

Every physician, ethicist, or legalist will agree that a person giving consent should be 'fully informed', 'free of coercion', and 'competent',[2] but there is no consensus on details to be provided during the process, nor the manner in which these should be delivered and documented. In 2011, the Advisory Committee on Organ Transplantation released a document with recommendations for the informed consent procedure in living organ donors in the United States. Although not legally binding, the committee recommended that each hospital involved in live organ donation should use a standardized informed consent form, adjusted to regional legislation. The document also provides a list of items that should be included in the educational process.[3] These forms have not yet been implemented in all transplant centers, but at least a written and signed consent is mandatory in many.[4] Unfortunately, the European situation differs from the American one. There are no European or nationwide guidelines, nor are there legal documents providing structured details on the informed consent procedure. Although there are many different policies and guidelines outlining matters that should be disclosed to potential donors, details are often not specified.[5,6] The actual documentation of consent also differs regionally; Spanish law for example, dictates that consent for live donation has to be obtained, documented, and signed in the presence of a judge,[7] while in Greece at least two witnesses have to sign a declaration of consent.[8]

These differences make it impossible for healthcare professionals to practice a uniform strategy, and it is challenging to determine which patient has received which information. Recent data from our group demonstrate that when tested on their knowledge, a large number of living kidney donors underestimate the complications and risks of live donor nephrectomy. Surman[9] published similar findings in renal and liver transplant patients, revealing significant conceptual limitations to their knowledge about their postoperative situation, underlining the importance of adequate preoperative education. Comparable results are demonstrated in other studies, where donors report varying degrees of (dis) satisfaction with and misunderstanding of provided information.[10] The question is raised whether the necessary information has not been provided correctly, whether donors simply do not understand or remember it, or, as has been proposed by some, whether they selectively filter information and thus miss particular risks associated with donation. Standardizing the informed consent procedure will help us better understand and address this matter. In light of ever-growing demands for safety, transparency, and documentation within the healthcare system, it can be expected that a standardized procedure will be legally mandatory in the near future.

The aim of this systematic review is to make an assessment of the informed consent procedure as it is described in the available literature, with regards to disclosed information, timing, documentation and donor comprehension of, and satisfaction with provided information. We hereby hope to address shortcomings and create the basis for a standardized procedure. In addition we will propose a concept to confirm donors' comprehension of the provided information.

RESULTS

Of the 1,009 articles identified in the initial search, 21 studies were included, consisting of 13 original articles and eight reviews. No additional studies were included after manually scrutinizing reference lists. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for systematic reviews is presented in Figure 1. Unfortunately, the quality of the included articles ranges from very low to low which can be explained by the fact that our systematic review consists of observational studies, automatically downgrading the level of evidence. The detailed assessment of the quality of the available evidence using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) tool is presented in Figure 2.

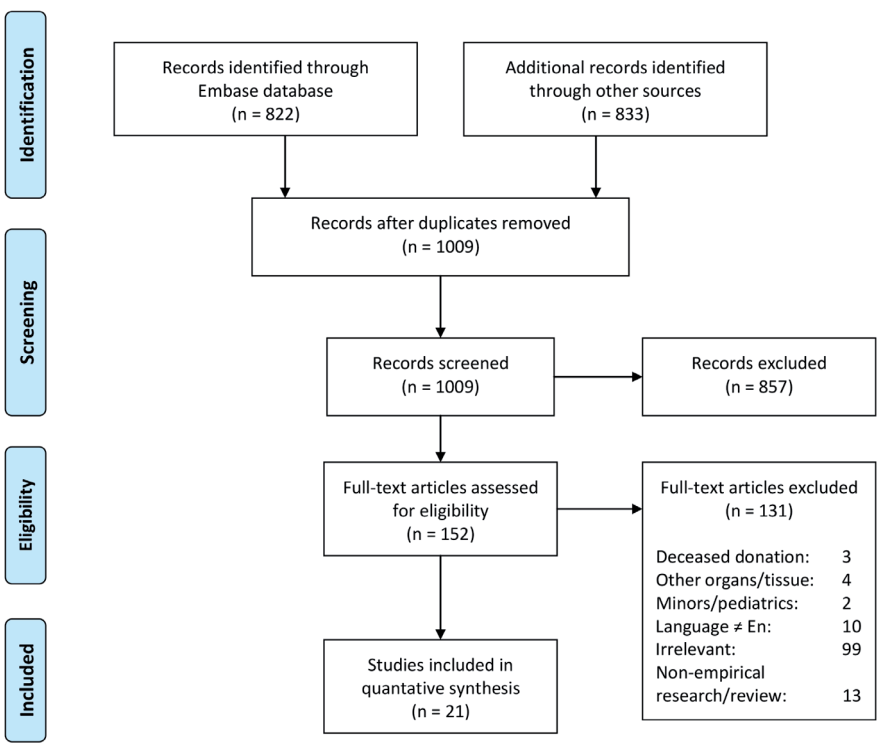

FIGURE 1. Flowchart of literature search, conducted January 17, 2014.

Informed Consent Procedure in Live Donor Nephrectomy

Patient or population: Live Kidney Donors
Settings: Several types of studies as listed below
Intervention: Informed Consent

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)
Donors Surveys/Interviews Follow-up: 42 years[1]	496 (5 studies[2])	⊕⊖⊖⊖ **very low**[3,4]
Medical professionals Surveys Follow-up: 2 years[5]	551 (3 studies[6])	⊕⊖⊖⊖ **very low**[3,7]
Informed Consent contents/procedure Follow-up: 9 years[8]	493 (5 studies[9])	⊕⊕⊖⊖ **low**[10]
Reviews Follow-up: 41 years[11]	0 (8 studies[12])	⊕⊖⊖⊖ **very low**

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Five studies, publication range 1970-2012
[2] Five survey/face to face interview studies
[3] Subjective information in surveys and interviews
[4] Great variations between donors
[5] Three surveys, publication range 2007-2008
[6] Three survey studies
[7] Great variations between practitioners/centers
[8] Five observational studies, publication range 2004-2013
[9] Three detailed analyses of informed consent forms/written information, two local process descriptions
[10] Objective analysis/description of materials or procedures
[11] Eight reviews, publication range 1971-2012
[12] Reviews

FIGURE 2. Appraisal of included studies, using the GRADE tool.

Informed consent process

Reviews

Table 1 summarizes the results of eight reviews published between 1971 and 2012,[10-17] including the country of origin and year of publication.

The main concern with informed consent in live organ donation is that hardly any research has been performed on the subject. Despite the importance of informed consent emphasized by all authors and the advice to implement standardized procedures documenting the donors' understanding of all risks and benefits, most hospitals have not yet done so, nor are there mandatory statutes issued by governments to ensure that hospitals live up to certain standards. Various authors compare living organ donors to medical research subjects.[15-18] Although they are essentially not that different in undergoing a medical procedure for the benefit of others, for the latter, strict rules and regulations apply and every research project is subject to extensive analysis by an independent institutional review board.[15,17] It can be assumed that no institutional review board would ever approve kidney removal as part of a research trial.[18] Multiple authors state that donors, contrary to research subjects, may not make a decision by care-

TABLE 1. Results of eight review articles investigating informed consent in live kidney donation.

Author, yr, country, LKD rate (%)[a]	General contents	Key topic	Conclusion
Gordon,[10] 2012 USA (43%)	Informed consent procedure	Living kidney and liver donors	Deficiencies in disclosure resulting in unmet information needs and poor comprehension of risks. Variability in transplant centers. Greater efforts are needed to improve the informed consent procedure.
Ciszek,[14] 2012 Poland (4%)	Ensuring donor safety	Living kidney donors	Standardized informed consent form should be introduced, expressing donors' full recognition of risks and benefits. It should enumerate types of info to be provided. Both verbal and written consent should be mandatory. Include non-medical specialists in process of information provision. Mismanaged communication may result in serious misconceptions and risks for donors and team members.
Petrini,[17] 2010 Italy (NK)	Informed consent	Living kidney donors	Comparison of research subjects with donors can improve informed consent procedure. Rigorous framework is crucial. Absolutely free and informed consent is illusory but continuous efforts have to be made to improve current situation. Validation of informed consent should be rigorous yet not overburdening.
Valapour,[13] 2008 USA (45%)	Understanding and validity of informed consent	Living kidney donors	Small number of empirical studies. Donors may not be fully informed at time of giving consent. Donor understanding of consequences of donation is an important area of investigation to improve informed consent process.
Mazaris,[12] 2006 United Kingdom (32%)	Ethical issues in kidney donation	All aspects of kidney donation	Only thoroughly informed donor can make voluntary decision. Intense debate on ethical issues in transplant community. Agreement would protect potential donors and ensure future of live kidney donation.
Kallich,[15] 1994 USA (38%)	Informed consent procedure, law, policy and ethics	Living organ donors	Transplant community needs to implement a series of policies and procedures that protect donors' right to make informed choice.
Adams,[16] 1987 USA (NK)	Informed consent, liability, medical ethics	All living organ donors	Donors should have all information a reasonable person would want plus any individual specific needs. Consent obtained based on misrepresentation or nondisclosure is invalid and may be seen as battery, but these days failure to disclose nature, risks or alternatives is mainly seen as professional negligence. Organ donor should enjoy as much protection as medical research subject.
Fellner,[11] 1971 USA (NK)	Psychological aspects of donor selection	Living kidney donors	Discrepancy between what the medical profession assumes the kidney donor experiences during the screening period and the actual perception. Most donors decide to donate immediately after being asked, special situation that cannot be compared to normal decision making. Initial decision has to be defended throughout waiting period for surgery.

[a]Living kidney donation rates in country of origin at time of publication. LKD, live kidney donation; NK, not known.

fully weighing risks and benefits but rather by emotional or moral reasoning.[11,13,19,20] Fellner[11] describes that there seems to be a discrepancy between what the potential kidney donor experiences during the screening period and what the medical team generally assumes. Instead of a deliberate balancing of risks and benefits, a simple yes-or-no decision is followed by an extensive waiting period and a feeling of having to defend the decision. Some authors believe that donors do not actually perceive all the information given to them, but rather focus on positive aspects to reaffirm their decision.[13] The question has been raised whether they actually understand all information provided to them, and it is argued that potential donors may not be fully informed at the time of consent.[10,12,13,15,21] Although this theory is somewhat confirmed by donors retrospectively reporting that they did not feel adequately informed about (some) aspects of kidney donation,[10,15] it has to be taken into account that the concept of live kidney donation has changed drastically since the 1970s. The live donor nephrectomy itself has been fully implemented in the general practice, and much more information has become available regarding outcome and possible perioperative and postoperative complications. Because of these developments, live kidney donation has gained ground over the past decades, and numbers are increasing worldwide; this merits a revisited opinion on information disclosure and consent. Although the informed consent process has evolved alongside the surgical procedure in an attempt to incorporate the most up to date knowledge and transfer it to potential donors in an understandable fashion, it still has to be brought to perfection. In addition, authors worry that psychosocial and financial aspects are neglected in the informed consent procedure, which is often led by medical specialists.[14,15] More research is needed to gain insight in what information should be provided to potential donors, by whom and in which manner to ensure optimal support in the decision making process, thereby safeguarding their autonomy.[10,15]

Original Articles

Thirteen original papers were identified (1970-2013). Table 2 provides an overview of the main characteristics and results of these studies, as well as the country of origin. Only a few studies have been performed assessing the informed consent procedure in live kidney donation. Most are surveys (N=5) among either medical professionals (N=3) or donors (N=2), or material (i.e., educational information, consent forms) or procedure analysis (N=4). In accordance with the reviews, considerable variations were observed between transplant centers and in some centers information provision was even deemed inadequate.[22] In one survey, a little over half of the respondents reported mentioning a certain risk of developing kidney failure but another 42% told donors that this risk was nonexistent or left it out completely.[23] Similar differences were encountered by other authors,[24] highlighting once again the need for a standardized procedure. Although these differences can be at least partially attributed to lack of evidence regarding the medical risks donors are exposed to after donor nephrectomy, it is alarming that potential donors receive different information in different centers.

Gordon[18] showed that some donors did not feel accurately informed about the postoperative risks and possible complications by the transplant team. Fellner[20] however, reported that all donors felt the information-giving process was more than adequate. Valapour *et al.*[25] described that although some

TABLE 2. Results of 13 original articles investigating informed consent in live kidney donation.

Author, yr, country, LKD rate (%)[a]	Study design	Topic	Study group (Response rate in %)	Main study parameter	Results/conclusion
Thiessen *et al.,*[4] 2013 USA (43%)	Inventory	Consent forms	143 unique forms (87%)	Inclusion of elements in consent forms	99% Obtains written consent. Need for uniform process
Gordon *et al.,*[29] 2012 USA (43%)	Inventory	Consent forms	332 forms (36%)	Reading levels of consent forms	Average reading level freshman college. Most transplant centers have failed to incorporate evidence based practices in informed consent forms.
Gordon,[18] 2012 USA (43%)	Interviews	LD experience	LD in postoperative period	Experience in general	LD felt uninformed about (rare) complications, although most had a positive experience.
Valapour *et al.,*[25] 2011 USA (44%)	Survey, retrospective	LD understanding	262 2-40 months after donation (74%)	Understanding of short- and long term risks	Good understanding recipient outcome, screening process and short term medical risks, less understanding of psychological risks, long term medical risks and financial risks. 94% Would donate again.
Sites *et al.,*[33] 2008 USA (45%)	Descriptive	IC process	One US hospital	Educational process	Extensive informed consent procedure, repetitive information provision, check of understanding, two week cooling off period.
Parekh *et al.,*[23] 2008 United Kingdom (36%)	Survey	Communication of risk factors	216 Health care professionals 40 countries, 177 centers	Methods and contents of risk conveying	Considerable variation in communication of risks between centers worldwide. 69% Written consent form. >90% Convey specific risk factors, great variation in contents.
Rodrigue *et al.,*[27] 2007 USA (44%)	Survey	General practice	132 US centers (64%)	IC process	30% Written consent prior to screening. 95% Written consent prior to surgery, other 5% verbal consent. 11% Cooling off period. Community would benefit from standardized process, improve public opinions and recipient access to live donation.
Housawi *et al.,*[24] 2007 Worldwide	Survey	Long term medical risks of kidney donation	203 transplant professionals worldwide	Communication of risk factors, surgeons vs. nephrologists	66% Written consent. >80% discusses hypertension, proteinuria, kidney failure; actual information varies (increased vs. not increased)

TABLE 2. (Continued)

Author, yr, country, LKD rate (%)[a]	Study design	Topic	Study group (Response rate in %)	Main study parameter	Results/conclusion
Lennerling and Nyberg,[22] 2004 Sweden (36%)	Inventory	Written LD information	16 information brochures from 14 countries	Provided information in brochures	Many brochures lack crucial information. Emotional decision making adequate information provision even more important. Great variation in hospital stay and sick leave, financial terms.
Wright *et al.,*[34] 2004 Canada (58%)	Descriptive	Donor evaluation process	One Canadian hospital	Donor evaluation/IC process	Process of confirming capacity to understand and consent, disclosure of information about the proposed procedure, donor understanding. Transparency of process and procedures & reflection on practice may encourage debate and permit openness and clarity.
Cabrer *et al.,*[28] 2003 Spain (NK)	Survey	LD experience	22 LDs from Spain six months after donation	Evaluation of quality of process perceived by LD	88% Understood evaluation period in retrospect. 95% Confirmed received information concurred with actual experience.
Fellner,[20] 1976 USA (NK)	Interviews	LD experience	12//22//148 (potential) LDs	Decision making process and overall experience	Decision making process immediate, prior to information gathering. Information-giving process more than adequate. Experience satisfying and meaningful, all would repeat process.
Fellner,[19] 1970 USA (NK)	Interviews	LD experience	20 LDs after donation, 10 planned LDs prior to donation	Decision making process and overall experience	23 LDs made decision immediately upon getting asked, before receiving all information. None opted-out after a long and repetitive information period. Decision making in donation is an early event preceding all information gathering and clarification.

[a]Living kidney donation rates in country of origin at time of publication. LKD, live kidney donation; RR, response rate; LD, living donors; IC, informed consent; NK, not known.

donors did report a lack of understanding of especially long-term (i.e. 48%), psychologic (31%), and financial risks (68%), this did not influence their theoretical willingness to donate again or negatively affect their experience, supporting Fellner's earlier conclusion that the decision making process in donors may differ from that in patients[19,20,25], which was later confirmed by Simmons *et al*..[26]

Contents of Informed Consent

Authors agree that although medical aspects of donation are usually well covered, psychosocial and financial aspects are much less frequently discussed.[22,23,27] Worsened familial relations associated with live kidney donation are reported in a small number of cases and up to 25% of donors deal with adverse financial effects.[28] The possibility of positive psychological outcomes is mentioned in about three quarters of the centers, whereas negative aspects are often neglected.[23] Parekh *et al.*[23] describe that informed consent in U.S. centers is mainly obtained by surgeons (74%). In non-U.S. centers surgeons are responsible for approximately 50% of the cases. Housawi *et al.*[24] presented similar rates with surgeons obtaining consent in 70% of donors. Table 3 demonstrates items that should, according to current literature and our own experience, be incorporated in a standardized informed consent procedure for live donor nephrectomy, and by whom they should be provided.

Many brochures and informed consent forms appear to be quite difficult to read. Gordon *et al.*[29] assessed 332 informed consent forms demonstrating an average college freshman reading level. This stands in marked contrast to recommendations that patient education materials should be written at an average of 5th to 8th grade primary school reading levels. Seeing this in perspective of our own living donor population, this may seem a bit harsh. The median age of our population is currently 53 years, and a recent cohort demonstrates that 56% of our donors have received further education after primary school (Timmerman *et al.*, unpublished data). Still, every donor needs to understand all provided information, and if nearly half of the population has only gone to primary school, college reading levels may be too difficult.

Timing of Information and Consent

Authors agree that information should be repetitive and provided at an early stage.[10,15]

Although most centers use presumed consent for the evaluation process, the Centers for Medicare and Medicaid Services require programs to have two separate informed consent processes; one for the screening period and one for the actual donor nephrectomy, the latter already being employed in most centers.[23,27] Many donors report that they decided to donate a kidney the first moment they heard about the option,[19,20] before receiving any information about the risks of the procedure. It is even more striking that none of them changed their mind after going through the extensive screening process. It is recommended that specific details of provided information are carefully documented on each donor contact. Although donor understanding is still not guaranteed, there will at least be more insight into the information-giving process.

Legal Aspects

The manner of providing information to (potential) donors and the method of acquiring informed consent is dependent on the local legal situation. Policies and laws vary enormously between different countries,[30,31] and in the United States even between different states.[27] In some regions, the donor's

signed informed consent is sufficient,[27] whereas others require witnesses or even a public authority to be present at the time of consent.[7,8,31] Even though informed consent is a standard requirement for live organ donation in most countries, some require additional justification.[31] In the Netherlands, the law on organ donation stems from May 1996 and is quite lenient on the matter of live organ donation. Consent has to be obtained in writing, signed and dated. This is further documented in the EU Directive (EU Directive 2010/53/EU for Living Organ Donation Practice)[32] which requires Member States to adhere to minimum standards in live organ donation (van Assche *et al.*, submitted).

Donor Experience

Few studies discuss donors' experience with the informed consent procedure,[18,25,28] and most are descriptive, retrospective studies or surveys. Fellner reports positive results in early studies dating back to the seventies, with all interviewed donors reporting the experience to be "the most meaningful of

TABLE 3. Elements to be included in a standardized informed consent procedure.

Category	Information	Details
Surgical information	Mortality	
	Major complications	Organ damage
		Bleeding
		Infectious complications
		Thromboembolic complications
	Minor complications	Pain
	Duration of hospital stay	Minor infectious complications
Medical information	Screening procedure	
	Long term effects	Chronic pain
		Hypertension
		Proteinuria
		Kidney failure
		Cardiovascular disease
	Risks of living with one kidney	Risk of malignancy in remaining kidney
	Follow up	Kidney trauma
Psychosocial information	Inflicted stress	
	Depression	
	Benefits	
	Potential impact on lifestyle	
Financial information	Expenses to be borne by donor	
	Potential impact on ability health- and life insurance	
	Potential impact on ability to future employment	
Other information	Voluntary nature	
	Legitimate ways out	Better quality kidney
	Recipient benefits	Shorter waiting time
	Risk of graft loss in recipient	
	Alternative donation procedures	
	Sick leave duration	

their lives".[19,20] More recent studies demonstrate that donors generally feel well informed and most of them would be willing to donate again with the information at hand.[25,28] Nonetheless, some donors do report various degrees of dissatisfaction with and misunderstanding of provided information. Gordon[18] published numerous living donor experiences. For some donors, it was the most meaningful experience of their lives; others look back on the ordeal with mixed feelings. Many donors felt, at least to some degree, unprepared for (adverse) postoperative events. Two donors reported a negative experience with donor education and informed consent: complication and mortality rates and long-term risks were inadequately described as were lifestyle adjustments and risks for the recipient. Another donor reports a similar experience, where she feels that "everything she learned about live kidney donation, she learned after her surgery", and regrets the blind trust she put in the transplant team. Yet another donor criticizes the media and medical industry for "only promoting the happily-ever-after stories", failing to investigate or share negative donor experiences. Another recurring statement in the donors' narratives was the postoperative realization that they were 'blinded' and thereby not quite informed at the time of giving consent: "I acknowledged my understanding, but never actually believed the rules applied to me", or: "I thought my consent was informed, but I eagerly heard what I wanted to hear – that I was eligible to donate".

DISCUSSION

With regulations in health care becoming even more strict, transplant teams are forced to reevaluate current practice concerning patient safety and informed consent, especially in living organ donors undergoing surgery for the benefit of others. Donor education, leading up to informed consent, needs to be carried out according to certain standards.

We performed a systematic review of the available literature to assess the existence and contents of these standards and whether transplant centers have actually implemented such procedures in their daily practice. We have included original articles and other reviews, thus creating a 'meta-review' of the available literature. To the best of our knowledge, ours is the first article that actually bundles all available evidence on the informed consent procedure in live kidney donation. This is therefore the first overview article that can serve as a basis for creating a standardized procedure. Although many authors touch on the subject, most do not actually describe the contents of the informed consent procedure. Little research has been performed, and available data show a great deal of variation in practice between different hospitals,[23,24] and even between different team members within one organization. Similar results were encountered when information brochures and informed consent forms from different centers were analyzed. In addition, these forms proved to be of an average college freshman reading level, which is much higher than the recommended level of 5th to 8th grade primary school.[29]

The most alarming finding however was the fact that, although a minority, some donors reported feeling misinformed, in some cases to such a degree that they felt the transplant team had lied to them regarding possible complications, long-term results and recipient outcome.[18] These donor experiences

are unacceptable and pose a threat to the success of a living donor transplant program. It is our responsibility to safeguard the informed consent procedure for live kidney donation by ensuring that potential donors are well educated and prepared for their upcoming procedure and postoperative course.

Although standardizing the informed consent procedure is a noble aim, there will inevitably be variations due to cultural, religious and educational differences between donors. Still, a standardized procedure will serve as a guideline, and alterations can be made according to the local population. Additional features can further support the educational system, and adjustments can be made according to local needs. Appointing independent donor advocates or involving a home-based educational team in the process could be of great value.[33-35]

Another point of interest is the fact that we cannot change the way donors perceive the information laid on them. Fellner was the first to demonstrate that most donors made the decision to donate upon the first moment of hearing of the option, and none of the interviewed donors had changed their mind after learning about all the risks associated with donating a kidney.[19,20] At the time these studies were conducted, live donation was performed only in family members. Donors may therefore have felt more pressure to donate because there were fewer options for their loved ones. Still, more recent studies confirm Fellner's earlier findings, and although much more knowledge is available regarding the nephrectomy, its outcomes, and possible adverse events, it is again suggested that donors do not actually use the provided information to make a deliberate decision, carefully weighing risks and benefits in a process eventually leading up to consenting or declining, but rather to reassure them that they have indeed made the right call.[13]

There are, unfortunately, few studies reporting on donor experience regarding education and consent in live kidney donation. In the field of live liver donation, a little more information is available, but results vary: some studies report donors' knowledge of the risks and benefits to be "good to very good", while some others report significant gaps in their knowledge.[36] Available information on kidney donors is anecdotal, and no reliable conclusions can be drawn, but it does give some insight in their perception of the information process. Although most donors considered donating to be a positive and meaningful experience and the main proportion would repeat the procedure if given the chance, quite a large percentage of donors report not being fully informed about (certain aspects of) the procedure.[18,25] Some donors report being well informed but simply thinking that the mentioned risks would not apply to them.[18] This not only further underlines the importance of adequate documentation to determine whether all donors have indeed received all the necessary information, it also warrants a new strategy to confirm donor comprehension. To assess whether the provided information has actually reached donors, a pop quiz could be administered to them at different moments in their screening process. A prospective trial using short questionnaires with open questions is currently being conducted in our center to assess whether this provides accurate information regarding donor comprehension. This will

give us more insight in which items of the informed consent process are covered adequately, and which need more specific attention. This then will guide us in creating a standardized procedure.

One of the foreseen problems with the incorporation of a standardized information and consent process is the heterogeneity of the potential donor pool. Striving for a worldwide standard format will therefore be virtually impossible, in light of political, cultural, and religious differences between countries and even populations within one geographical area. A standardized format can serve as a basis, and alterations can be made according to the local situation. Another objection physicians may have to the implementation of a standardized procedure is the extra labor that mandatory documentation will add to their workload. However, 82% of surveyed transplant centers worldwide would be willing to adopt centralized consent templates, with U.S. centers being slightly more willing than non-U.S. centers (79% vs. 84%, $P<0.001$).[23]

Limitations

A limitation and one of the major issues of this review is the fact that the available evidence is rather subjective and descriptive. Because donation procedures vary between regions, countries and centers,[37] as do informed consent procedures, published data are subject to interpretation in light of local practice. The contents of the informed consent procedure, and the manner in which information is provided, is dependent on local legislation and opinions on for instance ethics and religion. These opinions vary over time and per country, or even per region within a country.[37,38] Because the included studies comprise a wide time range and geographical area, results must be seen in perspective of these differences. In addition, local statistics on live donation, especially live donor nephrectomy complication rates and success rates in recipients, may influence not only the way medical practitioners inform potential donors but also the way that donors perceive this information and how they experience the donation process in general.

For this systematic review we have only included living kidney donors, as opposed to including all potential donors (i.e., liver, lung). Although the process of informed consent in live liver or lung donation is in many aspects similar to live kidney donation, complication rates in the former two are far greater than those in live kidney donation.

In addition, the geographical distribution of live liver and lung donation is different from live kidney donation. Although there are significant differences between countries regarding live kidney donation rates, this is still a much more common procedure. Live kidney donation was the first form of live donation to be performed, and informed consent procedures for the other organs may even be based on the procedures developed for kidney donation. Even so, the (also scarce) literature on informed consent in organ donation other than kidney similarly concludes that there are many variations in policy, opinions and donor comprehension, and consensus on best clinical practice is lacking.[36]

There are obviously many more ethical issues that should be addressed regarding live kidney donation, and may deserve attention during donor education and the informed consent procedure, but which are not included in this systematic review. Medical practitioners should ascertain themselves that there are no signs of coercion, and that the decision to donate is indeed voluntary. There is also the matter of paid donation, a currently much debated issue, on which opinions differ greatly.[39,40] However, these issues do not quite fall within the scope of this review and are therefore not pursued any further.

Looking at the assessment of the quality of the included studies, using the GRADE tool, we conclude that the evidence of each included study ranges from very low to low. Because the GRADE tool is primarily useful for assessment of interventional studies, the evidence scale is automatically downgraded since the published literature consists only of observational studies. Creating a protocol for a randomized controlled trial regarding the informed consent procedure is difficult and at risk for bias, and this has to the best of our knowledge not yet been initiated. It would, however, drastically improve the quality of evidence regarding the consent procedure.

In conclusion, it is clear that a standardized informed consent procedure in the live donor nephrectomy is much needed to ensure donor safety and satisfaction. It is to be expected that this will become legally mandatory, thereby protecting donors and physicians. It will further aid the transplant community in systematically providing and documenting information that will optimally prepare potential donors for the procedure and postoperative course. Once implemented it will serve as a basis in donor education and greatly benefit donors as well as medical practitioners.

The success of implementing a standardized procedure relies on input from transplant professionals from different centers and preferably different countries involved in live kidney donation. If an international working group were to be set up, local and regional protocols and guidelines could be combined to form a solid concept. The authors would like to invite those interested in participating in such a working group to contact us, preferably through e-mail correspondence.

MATERIALS AND METHODS

All aspects of the Cochrane Handbook for Interventional Systematic Reviews were followed, and the article was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[42] No review protocol was written in advance.

Literature search strategy

A comprehensive search was performed on January 17th 2014 in Embase, Medline OvidSP, Web-of-Science, PubMed, CENTRAL (The Cochrane Library 2014, issue 1) and Google Scholar. No date limits were used, so that no potentially relevant articles would be missed. Detailed search strings for each database are provided in Appendix 1 (see **SDC**, http://links.lww.com/TP/B95), no other limits were applied. All

references were screened by two independent reviewers (K.K., J.A.L.). If any discrepancies in inclusion or exclusion occurred, a senior investigator was consulted (F.J.M.F.D.). Study selection was accomplished through three phases of screening. During the first phase, the following types of studies were excluded: published conference abstracts and articles not presenting empirical research or reviews (e.g., personal commentary, letters to the editor). During the second phase, abstracts were reviewed for relevance, and the full-text articles were obtained. In the last phase, full-text articles were reviewed; requirements for inclusion were a description of the informed consent procedure in live donor nephrectomy. Manual reference checks were performed to search for potentially missing studies. No authors were contacted to provide full-text articles, because all included articles were obtained in full-text. Articles not written in English were excluded to prevent translational bias.

Data extraction and critical appraisal

Data extraction was performed by two authors (K.K., J.A.L.). Again, if any discrepancies occurred, consensus was reached after consulting a senior investigator (F.J.M.F.D.). The level of evidence of each paper was established using the GRADE tool.[43] The GRADE approach defines the quality of a body of evidence by consideration of risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias.

ACKNOWLEDGEMENTS

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Chapter 5

Systematic review and meta-analysis of the relation between body mass index and short-term donor outcome of laparoscopic donor nephrectomy

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ABSTRACT

In this era of organ donor shortage, live kidney donation has been proven to increase the donor pool; however, it is extremely important to make careful decisions in the selection of possible live donors. A body mass index (BMI) above 35 is generally considered as a relative contraindication for donation. To address whether this is justified, a systematic review and meta-analysis were carried out to compare perioperative outcome of live donor nephrectomy between donors with high and low BMI. A comprehensive literature search was performed in MEDLINE, Embase, and CENTRAL (the Cochrane Library). All aspects of the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement were followed. Of 14 studies reviewed, eight perioperative donor outcome measures were meta-analyzed, and, of these, five were not different between BMI categories. Three found significant differences in favor of low BMI (29.9 and less) donors with significant mean differences in operation duration (16.9 min (confidence interval (CI) 9.1-24.8)), mean difference in rise in serum creatinine (0.05 mg/dl (CI 0.01-0.09)), and risk ratio for conversion (1.69 (CI 1.12-2.56)). Thus, a high body mass index (BMI) alone is no contraindication for live kidney donation regarding short-term outcome.

Kidney transplantation is the treatment of choice for end-stage renal disease.[1] In the United States, more than 88,000 people are currently on the waiting list for a kidney transplant. However, in 2010, only 16,898 patients received a donor kidney, of which 37% were from a live donor. However, end-stage renal disease patients are dependent on hemodialysis or peritoneal dialysis, which in itself has a high morbidity and mortality rate.[2-5] After kidney transplant, life expectancy and the quality of life improve markedly.[6] As the deceased donor pool remains more or less stable, and the donor shortage increases, it is important to assess whether the live kidney donor pool can be expanded. Careful decisions with respect to including and excluding criteria for possible live donors are warranted.

In the Erasmus MC, Rotterdam, The Netherlands, in 2010 135 kidney transplantations were performed with kidneys from a live donor (75% of the total). Especially in a program of this magnitude, the need for careful donor selection is of critical importance. One of the parameters used for donor selection is the BMI. In most transplant centers, a BMI higher than 35 is considered a relative contraindication for donation,[7,8] which is in accordance with the guidelines formulated during the Amsterdam Forum in 2005[9] and other international guidelines.[10-12] This is because donors with a higher BMI are said to be more prone to complications.[13,14] Furthermore, obesity is correlated with chronic kidney disease[15,16] and with several risk factors for kidney disease, such as diabetes, cardiovascular diseases, and hypertension. In addition, a BMI higher than 30 may predispose for more postoperative pain.[17,18] However, the level of evidence of published studies may not be sufficient to answer the question whether a high BMI leads to more complications of live donor nephrectomy (LDN). The incidence of obesity is increasing in the general population, and thus in possible live kidney donors. Lumsdaine *et al.*[19] carried out a survey in the United Kingdom and demonstrated that only one center accepted donors with a BMI greater than 30 in 1999. Six years later, a US survey reported that in 10 years the acceptance of a donor with a BMI higher than 30 had increased from 86 to 90%.[20] On the basis of these numbers, we conclude that in most centers obesity is no longer considered a contraindication. The question is whether or not BMI is a reliable parameter for the selection of live kidney donors. The aim of this review is to evaluate the literature systematically to examine the relation between BMI and outcome of LDN. We aimed to specifically investigate perioperative outcome measures and did not focus on long-term outcome as there is little literature available.

RESULTS

Study selection

Publications were selected for review if they investigated two or more groups of donors divided into BMI categories. Of the 529 publications found after the initial search, 102 publications were screened according to abstract or full text. After screening, 14 publications fell in the scope of our study. One article was excluded because of missing s.d. values.[21] Fourteen studies were included for review and meta-analysis. Three additional articles were found by scrutinizing the reference lists.[22-24] These three articles were not identified in the original search, because these were conference abstracts or were not

indexed. A flow diagram is presented in Figure 1. The characteristics of included studies are presented in Table 1. A detailed morbidity report of all included studies is available in Supplementary Data online. Not all studies used the same cutoff value for BMI according to standards set by the World Health Organization.[25] After careful consideration, consensus was reached to compare all studies based on 'high BMI' versus 'low BMI'. For the pooled cohorts, a BMI of 29.9 was used as the cutoff value, according to the World Health Organization definitions. Furthermore, we chose this value because the prevalence of overweight is relatively high in developed countries. To adequately differentiate between donor BMI groups, we classified a BMI >30 as 'high BMI'.

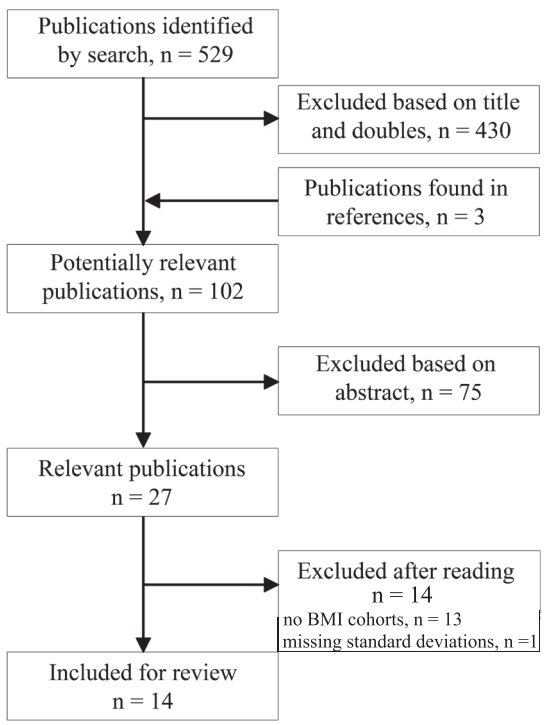

FIGURE 1. Flow diagram outlining selection of studies.

Operative outcome measures

The operation duration of laparoscopic LDN was investigated in eight studies.[23,26-32] All studies showed a longer operation time in the high BMI group, except for one. The overall mean difference, based on a total of 1105 observations was 16.9 min (CI 9.06-24.76; *P*<0.0001) in favor of donors with a low BMI (Figure 2). The incidence of conversion from laparoscopic LDN to an open procedure was assessed in seven studies, which included a total of 5869 patients.[22,27-29,31-33] All studies found a risk ratio higher than 1 for donors with a high BMI. Overall, there is a risk ratio of 1.69 (CI 1.12-2.56; *P*=0.01) (Figure 3). The duration

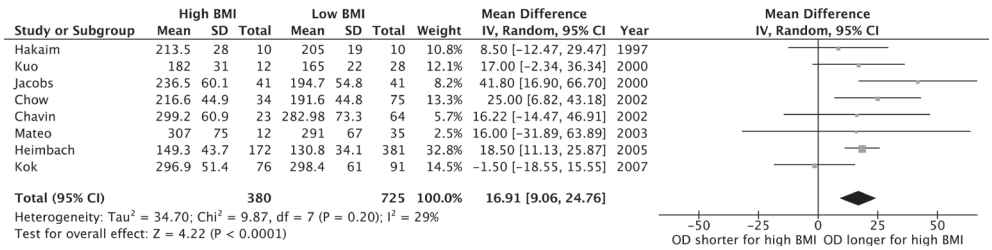

FIGURE 2. Forest plot of comparison: high versus low BMI donors, outcome: operation duration (OD) in minutes. BMI, body mass index; CI, confidence interval.

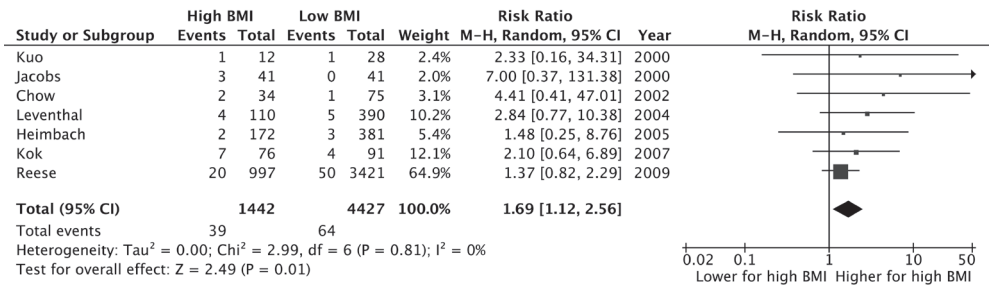

FIGURE 3. Forest plot of comparison: high versus low BMI donors, outcome: conversion (risk ratio). BMI, body mass index; CI, confidence interval.

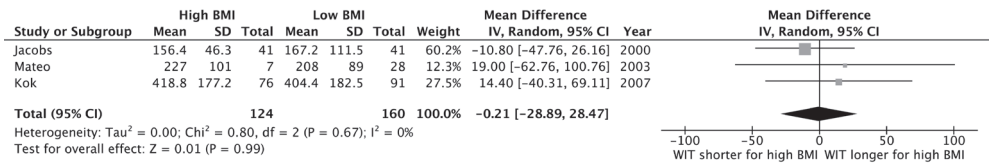

FIGURE 4. Forest plot of comparison: high versus low BMI donors, outcome: warm ischemia time (WIT) in seconds. BMI, body mass index; CI, confidence interval.

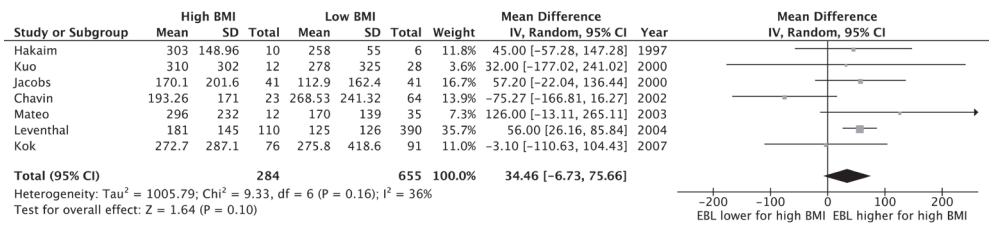

FIGURE 5. Forest plot of comparison: high versus low BMI donors, outcome: estimated blood loss (EBL) in millilitres. BMI, body mass index; CI, confidence interval.

of the warm ischemia in seconds was assessed in three studies.[28,30,32] All studies except for one reported a longer warm ischemia time for donors with a high BMI. Overall, the meta-analysis shows no significant difference between groups (mean difference: -0.21 s (CI -28.89-28.47; *P*=0.99) based on 284 observations (Figure 4). Seven studies investigated the estimated blood loss in millilitres during LDN, in a total of 939

donors.[22,23,26-28,30,32] Five studies reported more blood loss in the high BMI group. However, in two studies, less blood loss was observed in the group with high BMI donors. Overall, the meta-analysis shows no significant difference between groups (mean difference = 34.46 ml; CI -6.73-75.66; *P*=0.10) (Figure 5).

Perioperative outcome measures

The length of hospital stay after LDN was investigated in 10 studies in a total of 6019 patients.[22,23,26-33] Eight studies showed a longer length of stay in the high BMI group. Two studies found a shorter length of stay for the group with high BMI, and one reported no difference. Overall, there is no significant difference between groups (mean difference = 0.18 days; CI -0.02-0.39; *P*=0.08) (Figure 6). The amount of perioperative complications, such as bleeding, wound complications, urinary tract infections, readmission, and reoperation, was assessed in eight studies, in a total of 5869 patients.[22,27-29,31-33] Three studies reported a higher risk of complications for donors with a high BMI. Overall, the meta-analysis shows no significant difference between groups (risk ratio=1.01; CI 0.75-1.36; *P*=0.94) (Figure 7).

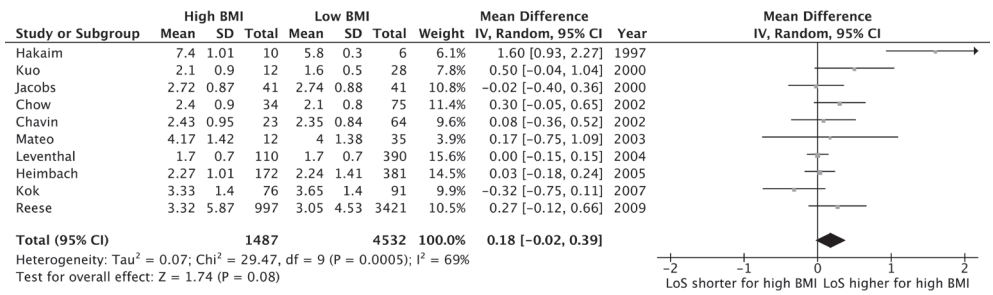

FIGURE 6. Forest plot of comparison: high versus low BMI donors, outcome: length of stay (LoS) in days. BMI, body mass index; CI, confidence interval.

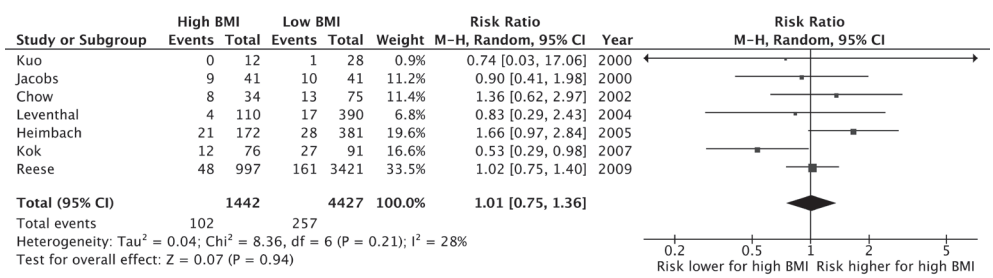

FIGURE 7. Forest plot of comparison: high versus low BMI donors, outcome: perioperative complications (risk ratio). BMI, body mass index; CI, confidence interval.

Kidney function outcome measures

The difference in preoperative and postoperative serum creatinine in mg/dl was analyzed in eight studies in a total of 3511 patients.[24,27,30,31,33-36] Although not all studies reported the exact time points of

serum measurements postoperatively, best matches were acquired for optimal comparison. Five studies reported a higher increase in serum creatinine in the group with high BMI donors. Two studies showed no mean difference, and one study reported a lower increase in the group with high BMI donors. Overall, the meta-analysis shows a mean difference of 0.05 mg/dl (0.01-0.09; *P*=0.02) in favor of low BMI donors (Figure 8). Four studies assessed the change in glomerular filtration rate after LDN at different time points after donor nephrectomy. All except one reported a greater decrease in glomerular filtration rate (GFR) in the group with high BMI donors. Overall, the meta-analysis shows a mean difference of 1.78 ml/min (-1.62-5.18; *P*=0.31) (Figure 9).

An additional subgroup analysis was performed to gain better insight into differences within the high BMI group. Three studies of our original analysis could be used,[23,31,33] as they described multiple cohorts. Kidney donors with a BMI of 30-34.9 were compared with those with a BMI of 35 and higher. For none of the outcome measures were significant differences found between these BMI groups based on a meta-analysis (data not shown). A total of 1192 donors were analyzed in this respect.

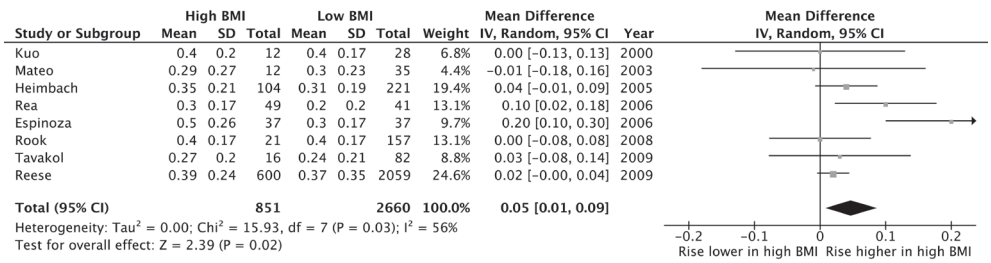

FIGURE 8. Forest plot of comparison: high versus low BMI donors, outcome: difference in serum creatinine in mg/dl. BMI, body mass index; CI, confidence interval.

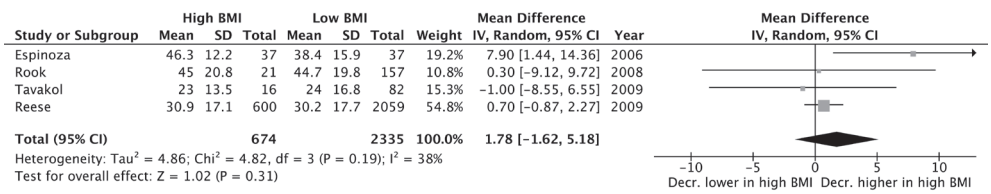

FIGURE 9. Forest plot of comparison: high versus low BMI donors, outcome: decrease in glomerular filtration rate in ml/min. BMI, body mass index; CI, confidence interval; Decr., decrease.

TABLE 1. Characteristics of studies comparing outcome of LDN between BMI groups.

Reference	Study type	Groups (BMI)	*N*	NOS	Outcome measures	Follow-up
Hakaim *et al.*[26]	Retrospective cohort	IBW FAIBW MAIBW	6 5 5	6	OD, EBL, CI, UP, FD, SCr	2 Months
Jacobs *et al.*[28]	Retrospective cohort	<30 >35	41 41	7	OD, C, DR, LP	1 Week
Kuo *et al.*[27]	Retrospective cohort	≤31 >31	28 12	8	OD, EBL, LoS, SC	4.2 ± 0.4 Months
Chavin *et al.*[23]	Retro/ prospective cohort	17-25 25-27 27-30 30-35 35-40	28 17 19 16 7	7	LoS, OD, EBL, ME	Not reported
Chow *et al.*[29]	Prospective cohort	<30 ≥30	75 34	6	OD, C, SC, LoS	Not reported
Mateo *et al.*[30]	Prospective cohort	<30 ≥30	35 12	8	WIT, OD, EBL, UP, LoS, SCr	
Leventhal *et al.*[22]	Retrospective cohort	≤30 >30	390 110	7	EBL, LoS, SC, C	Not reported
Heimbach *et al.*[31]	Retrospective cohort	<25 25≤BMI<30 30≤BMI<35 ≥35	170 211 114 58	8	C, OD, LoS, SC, SCr, BP	11 ± 0.34 Months
Espinoza *et al.*[24]	Prospective cohort	20≤BMI≤25 >30	37 37	6	SCr, GFR, SC, M	50.8 ± 28.5 Months
Rea *et al.*[34]	Retrospective cohort	<30 ≥30	41 49	8	SCr, BP	Median 340 (21-963) days
Kok *et al.*[32]	Prospective cohort	<25 >27	91 76	8	C, WIT, OD, EBL, SC, LoS, PC	1 Year
Rook *et al.*[35]	Retrospective cohort	<25 25-29.9 ≥30	87 70 21	7	GFR, SCr	2 Months
Tavakol *et al.*[36]	Retrospective cohort	<30 ≥30	82 16	8	GFR, 24-h ur.prot., SCr, HT, Chol, BP	11 ± 7 Years
Reese *et al.*[33]	Retrospective cohort	<25 25≤BMI<30 30≤BMI<35 ≥35	2002 2108 944 250	6	LoS, SCr, C, SC, GFR, HT	1 Year

Abbreviations: BP, blood pressure; C, conversion; Chol, cholesterol; CI, crystalloid infusion; DR, donor recovery; EBL, estimated blood loss; FD, furosemide dose; F/MAIBW, female/male above ideal body weight; GFR, glomerular filtration rate; HT, hypertension; IBW, ideal body weight; M, mortality; ME, morphine equivalents; LoS, length of stay; LP, laparoscopic ports; Nos, Newcastle–Ottawa Scale, SCr, serum creatinine; OD, operation duration; PC, postoperative complications; SC, surgical complications; UP, urine production; WIT, warm ischemia time.

Follow-up is in years±s.d. unless otherwise reported.

DISCUSSION

In the literature, there seems to be a slowly increasing trend of accepting overweight people as live kidney donors.[20,22,31,37,38] By conducting this review and meta-analysis, we aimed to obtain a better insight into the relationship that exists between BMI and short-term outcome after LDN. To compare all groups described in the studies, we justified pooling the cohorts for mathematical reasons, being aware of the possible implications and limitations such as statistical bias and heterogeneity. Of the studies included, 14 examined obese living donors based on their BMI class. Five studies used a cutoff value of 29.9 kg/m^2 for high versus low BMI,[22,29,30,34,36] according to the World Health Organization classification. In four studies, more than two cohorts of BMI categories were defined, but from these we were able to pool the cohorts into two cohorts with a cutoff value of 29.9 kg/m^2.[23,31,33,35] The other five studies used a different cutoff point (summarized in Table 1). To include as many studies as is statistically valid, a consensus was reached to pool these data with the two BMI groups. Nine studies were retrospective cohort studies, one collected retrospective and prospective data,[23] and four were prospective cohort studies.

Several authors have already indicated the advantages of laparoscopic LDN over the open approach.[39-44] The BMI was taken into account in some of these studies; however, no hard statements were made regarding the relation between BMI and outcome of LDN. We aimed to include only those studies that assessed laparoscopic LDN to enable the most sound comparison; however, in some publications, we were unable to identify whether a laparoscopic or an open LDN had been performed.[24,26,35,36] As significance did not change whether we included or excluded these studies, we decided to include them in the analysis. A meta-analysis by Young *et al.*[45] performed in 2008 also partially investigated the influence of BMI on outcome after LDN. Only a limited number of outcome measures, i.e., operative time, blood loss, and length of hospital stay, were meta-analyzed. Differences in serum creatinine and GFR were summarized, but not meta-analyzed. The authors concluded that more research should be conducted to investigate whether high-risk donors can be safely accepted for live kidney donation.

In 2010, Friedman *et al.*[46] reported that obesity is associated with a higher complication rate. However, as commented in the article, complications are not segregated by severity and thus can consist of a large number of minor complications. Segev *et al.*[47] demonstrated in 2010 that no statistically significant difference in surgical mortality was observed by BMI. Overall, various outcome have been reported in literature and this emphasizes the need for a systematic review.

According to this systematic review and meta-analysis, only in three out of eight short-term outcome measures were significant differences seen between low and high BMI donors. With regard to the operative outcome measures, only operation duration and conversion rate were significantly lower in favor of low BMI donors. Importantly, no higher complication rates were found in the high BMI group. The fact that operation duration is longer for high BMI donors is plausible, as in this group the operation is technically more challenging because of more (perirenal) fat and more difficulties in identifying the vessels in the hilum.[48,49] The overall difference in operation duration found in our meta-analysis is only 17 min,

which is not necessarily of great clinical relevance. Furthermore, there is no evidence in the literature that such a small increase of general anesthesia time has disadvantages for a patient. Low BMI donors were found to have a significantly lower conversion rate compared with the high BMI group. Nowadays, the overall conversion rate from laparoscopic LDN to the open approach is very low. Large case series nowadays report a conversion rate of 0.6-0.7%.[50,51] In the studies we included, conversion rates for high BMI donors range from 1.2 to 9.2%. In our opinion, a conversion rate of 9.2% is very high; however, we should take into account that experience and laparoscopic skills have increased over the years. However, although conversion rates are higher for the high BMI donors, it does not seem to affect complication rates and length of hospital stay. The difference found in warm ischemia time is not significant between donor groups. In 2006, Simforoosh *et al.*[52] showed in a prospective study that prolonged warm ischemia time up to 17 min does not lead to impaired graft function, which was confirmed in another retrospective study.[53] However, these studies did not include donors with a BMI >30.

Of the two perioperative outcome measures, none was significantly different between BMI groups. In 2005, Bachmann *et al.* described that obese donors have significantly higher visual analog scale scores compared with donors with a normal weight.[17] Visual analog scale scores were not reported in included studies and therefore not a part of our meta-analysis. However, it appears that the higher conversion rate in high BMI donors does not lead to more postoperative pain necessitating longer hospital stay.

Authors describing their early LDN experience report higher complication rates in donors with BMI >30.[54,55] More recent publications show that overall complication rates of LDN range from 4 to 30%,[44,56] which is in line with the complication rates we found. One could argue that the included studies in our analysis are hard to compare because not all of them assessed the same type of complications. Therefore, we decided to pool complication data into one group, i.e., perioperative complications, and found no difference between BMI cohorts.

Five of the included studies in the review reported zero donor deaths, and the other nine did not report on mortality.

A statistically significant difference in increase of postoperative serum creatinine was found, but no difference was found in GFR between the two BMI groups. A study conducted by Rizvi *et al.*[57] also shows that obese donors have no greater decline in GFR compared with nonobese donors.

Tavakol *et al.*[36] and Reese *et al.*[33] assessed kidney function using the estimated GFR calculated with the modification of diet in renal diseases equation.[58] As this is an estimation of the GFR, reported values may differ from the actual GFR.

We should acknowledge the fact that not all of the included studies used the same postoperative schedule of follow-up visits for the donors.

Limitations

A concern that could not be entirely analyzed is the long-term effect of LDN on overweight or obese live kidney donors. Even though this was not the primary aim of our meta-analysis, we felt the need to

address this matter. The main reason why clinicians are reluctant to include high BMI donors is because of the increased risk for the metabolic syndrome. Hsu *et al.*[59] showed in 2006 that, with increasing BMI, the relative risk of developing end-stage renal disease is also increasing. Persons with a BMI between 30 and 34.9 already have an adjusted risk ratio of 3.57. However, we should note that the subjects described were people with a high BMI and not a highly selected group of live kidney donors with a high BMI (and thus otherwise healthy). Interestingly, Ibrahim *et al.*[60] demonstrated in 2009 that, overall, kidney donors have a better long-term outcome in terms of developing end-stage renal disease than do nondonors and that no major elevations in serum creatinine occur even 30 years after donation. Hypertension and estimated GFR < 60 were associated with BMI, however with relatively low odds ratios (both 1.12). Recent data by Tent *et al.*[61] demonstrate that, in 100 donors (5-year follow-up), only the filtration fraction is significantly higher compared with that before donation. However, the filtration fraction is equal to that of the lean donors and is therefore not determined by BMI. Wu *et al.*[62] reported no significant difference in the 3-year follow-up of serum creatinine and blood pressure between low and high BMI donors. Amin *et al.*[63] stated that obese kidney donors are not at higher risk for renal dysfunction but do have an increased incidence of several cardiovascular disease risk factors. However, the number of analyzed donors is small. Aggarwal *et al.*[64] showed that, at 1 year post donation, there is no increased incidence of hypertension, proteinuria, or renal dysfunction in obese kidney donors compared with nonobese donors.

Our meta-analysis combines data across studies to prove that at least the short-term outcome of high BMI kidney donors is acceptable. The main limitation of this meta-analysis, as with any overview, is that the outcome definitions (for serum creatinine, GFR, and complications) are not the same across studies. Sensitivity analyses were performed to check whether the results remained significant (or gained significance). Publication bias might account for some of the effects we observed. The comprehensive search in multiple databases and extensive scrutinizing of the reference lists minimized the presence of publication bias. On exploring heterogeneity using funnel plots and χ^2 and inconsistency (I^2) statistics, significant heterogeneity was found to be minimal.

Despite our conclusion that BMI only correlates with three outcome measures, we still advise that obese patients be encouraged to lose weight before kidney donation and be excluded if they have other associated comorbidities. Meticulous postoperative follow-up, and prevention of weight gain of these donors would be very important. In line with this, according to several international guidelines, every person with a BMI above 40 or a BMI higher than 35 with comorbidities should be advised to undergo bariatric surgery.[65-67] Furthermore, as we do not know the exact number of donors with a BMI over 40 in our analysis, we should be careful in stating that a BMI higher than this value is no contraindication for LDN. Obese donors should be informed about possible risks, such as the general risk of complications during surgery. In addition to this, healthy lifestyle education should be available to all living donors.[9]

Overall, on the basis of the results of our systemic review and meta-analysis, we conclude, regarding short-term outcome, that a high BMI in itself is no contraindication for LDN. However, as long-term data are still scarce, careful selection of possible live kidney donors is of considerable importance.

MATERIALS AND METHODS

All aspects of the Cochrane Handbook for Interventional Systematic Reviews were followed and the study was written according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[11]

Literature search strategy

A comprehensive database search was carried out. The following databases were searched from inception to January 2011: MEDLINE, Embase, and CENTRAL (the Cochrane Library 2011). Search terms were: (Living Donors [Mesh] AND "Body Weights and Measures"[Mesh]) OR (donor AND nephrectomy AND BMI) in PubMed. Other databases were searched with comparable terms, suitable for the specific database. We focused on the outcome of LDN and therefore excluded publications describing graft function or outcome in kidney transplant recipients. Additional articles or abstracts were retrieved by manually searching the reference lists of relevant publications. We excluded studies that assessed LDN using the open approach, as it is known that (post)operative outcome is significantly different than that of laparoscopic LDN.[40]

Literature screening

Studies were evaluated for inclusion by two independent reviewers for relevance to the subject. Study selection was accomplished through three levels of screening. At the first level, studies were excluded on the basis of title and if they were one of the following: review, case report, or comments. In addition, different studies describing the same population were excluded. At the second level, all abstracts were screened for relevance. If the abstract contained an indication that the article had several BMI cohorts, it was moved to the third level. For publications with no abstract, the full text was acquired. In level three, inclusion required that studies describe two or more groups of donors that were selected on the basis of their BMI or body weight and had relevant outcome measures in the donors.

Data extraction and critical appraisal

Data extraction was performed using electronic forms by two authors independently (JAL/SMH). All data regarding outcome in donors were extracted. Study authors were contacted to supply additional data or missing s.d.'s. In studies in which medians and ranges were given, raw data was requested to calculate means and s.d.'s. The quality of studies was assessed according to the Newcastle-Ottawa Scale

for observational and cohort studies, which score selection, comparability, and outcome. Studies should have a Newcastle-Ottawa Scale-score equal to or greater than 6 in order to be included.[68]

Statistical analysis

A meta-analysis was performed by using Review Manager version 5.1 (The Nordic Cochrane Center, Copenhagen, Denmark). Random-effects models were used.[69] Depending on the outcome, results were presented in forest plots with risk ratios or mean differences. Overall effects were determined using the Z-test. Ninety-five percent confidence intervals of these values were given and $P<0.05$ was considered statistically significant. Heterogeneity between studies was assessed by three methods. First, a Tau^2 test and a χ^2 test were conducted for statistical heterogeneity, with $P<0.05$ being considered statistically significant. In addition, I^2 statistics were used to assess clinical heterogeneity.[70] Some cohort studies could not be analyzed at first because of the fact that there were more than two cohorts.[23,26,31,33,35] To compare these studies, cohorts were pooled, and new means and s.d.'s were calculated.[18] Group means were weighted by the number of donors in each study group. Variance estimates for pre- to post-donation changes in outcomes were not reported in all studies; they were calculated as $\sigma^2_{\Delta} = \sigma^2_{pre} + \sigma^2_{post} - 2\rho\sigma_{pre}\sigma_{post}$ where ρ represents the correlation between the pre- and post-donation values. A correlation of 0.5 was used to impute the missing change variance estimates.[71]

DISCLOSURE

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

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Chapter 6

Perirenal and Intra-Abdominal Fat Mass Superior over BMI in Predicting Donor Outcome in Laparoscopic Donor Nephrectomy

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ABSTRACT

Background The predictive value of the Body Mass Index (BMI) on outcome of laparoscopic donor nephrectomy (LDN) is still under debate. We hypothesized that other parameters, such as intra-abdominal or perirenal fat mass, may have a stronger correlation with perioperative complications and long-term results of LDN and kidney transplantation.

Methods A retrospective database and preoperative imaging review was conducted on all live kidney donors who underwent laparoscopic live donor nephrectomy from 2004 until 2013 in the center of the authors. Out of 620 donors, preoperative abdominal CT or MR imaging was available. Automated volumetric measurement of the amount of perirenal fat in mm^3 was carried out based on CT-scans. As a validation, several linear measurements of abdominal visceral fat (IAF-measurements) were performed on both CT (-as MRI-scans). These data were correlated with several outcome measures of LDN and renal transplantation in both univariable and multivariable regression models.

Results As expected, the BMI correlates with some outcome measures of LDN. However, the volume of perirenal fat demonstrates a stronger correlation in even more outcome measures in univariable and multivariable regression: operation duration ($P<0.001$), estimated blood loss ($P<0.001$), and difference in serum creatinine ($P<0.001$) and estimated GFR ($P=0.002$) at 1 year postdonation. Furthermore, the IAF-measurements show the same significant correlation, both in the CT-cohort as in the MRI-cohort.

Conclusion In this large cohort of live kidney donors, we have confirmed that BMI alone is not the best predictor for outcome of LDN. Importantly, since the IAF is a linear measurement, no complex software is required. Therefore, we conclude that the measurement of intra-abdominal fat is a useful additional parameter in predicting peri- and postoperative outcome of LDN and should be included in the assessment of possible live kidney donors.

INTRODUCTION

Live donor nephrectomy has proven to successfully increase the donor pool. However, as the incidence of the Body Mass Index (BMI) rises in the general population, so does the BMI of potential live kidney donors. BMI and its relation with outcome of laparoscopic donor nephrectomy (LDN) is widely discussed in literature, reviewed by Lafranca *et al.* in 2013.[1] Already the acceptance of high BMI donors is increasing, which is one of the so-called 'extended criteria' of live kidney donors that becomes more and more accepted.[2,3] Remarkably, in 2012, Lennerling *et al.* showed that a BMI above 35 is considered as an absolute contraindication for donation in more than 44% of the transplant centers.[4] Furthermore, a survey carried out by Klop *et al.* shows that still 25% of the European transplant centers decline donors with a BMI>30.[5]

The Erasmus MC, University Medical Center Rotterdam harbours the largest live kidney donor transplantation programme in Europe. Over 150 laparoscopic donor nephrectomies are performed every year and this number will further expand in the future. The still existing donor organ shortage urges us to focus on ways to expand our donor pool. It is therefore crucial to closely examine current criteria for kidney donation and broaden or fine-tune these criteria where possible.[3] However, since a live kidney donor is generally in good health, we should carefully select our possible donors, to ensure that a healthy person does not become a patient. Regarding short-term outcome multiple studies have been carried out, showing that (when data is pooled), outcome is not negatively influenced by a high BMI.[1] However data on long-term outcome are scarce in terms of numbers of donor outcome.[6-10]

Therefore, we argued there might be other parameters influencing outcome of overweight or obese donors. Only a few studies have been carried out to investigate the role of the preserved volume of the kidney on postdonation outcome. Jeon *et al.* showed that a lower preoperative kidney volume is a significant predictor of delayed kidney function recovery.[11] Yakoubi *et al.* confirmed that the preserved kidney volume correlates with postdonation estimated glomerular filtration rate (eGFR) at 1 year ($P< 0.001$).[12] The preserved kidney volume ratio, however, did not correlate with kidney function. Some other studies confirm above findings.[13]

As BMI does not take the fat distribution into account, we hypothesised that the amount of intra-abdominal and more specifically, perirenal fat, could play a role in outcome. In 2008, Anderson *et al.* already described a correlation between the amount of perirenal fat mass and operative time in LDN, however, only linear measurements were performed.[14] We decided to use this concept and investigate it further in a three-dimensional way.

METHODS

Software FatSequence; can calculate volumetrics based on CT-scans.

Study population From August 2005 until November 2012, 168 preoperative CT-scans were retrospectively reviewed of donors that underwent transperitoneal laparoscopic donor nephrectomy. Since the

gold standard for preoperative imaging prior to 2010 used to be MRI-imaging, we had limited CT-scans available up until 2010. All donors with a preoperative CT-scan were considered eligible to include in the volumetric analyses. Exclusion criteria were: other operation techniques than the transperitoneal laparoscopic approach (mini-open, hand-assisted retroperitoneoscopic, or robot-assisted donor nephrectomy). In order to expand our cohort, all preoperative MRI-scans from donations between 2005 and 2013 were also included (n = 452), leading to a total of 620 donors. As not only donor outcome is essential, we investigated the outcome of their respective renal transplant recipients as well.

Outcome measures donors Operation duration, warm ischemia time (WIT), estimated blood loss, hospital stay, conversion and difference in preoperative serum creatinine levels and eGFR compared with one year after donation.

Outcome measures recipients Operation duration, WIT, estimated blood loss, length of stay, difference in serum creatinine, delayed graft function (DGF), primary non function (PNF), diuresis directly after reperfusion, insertion of percutaneous nephrostomies, complication rate, thrombosis rate, graft- and patient survival.

MEASUREMENTS

CT-scans (n = 168) The perirenal fat of both kidneys was measured with a volumetric measurement in mm^3 using the aforementioned software. The volumetric measurement was calculated by drawing the circumference of Gerota's fascia surrounding the kidney in all slices from the most cranial slice where the kidney was visible on the CT-scan to the most caudal slice. The software automatically calculated the volume in mm^3 (Figure 1). Furthermore, the total amount in mm^2 of subcutaneous fat (Figure 2) and visceral fat (Figure 3) was measured in one slice at the level of the origin of the superior mesenteric artery. Additionally, the distance in mm was measured between the aorta and the linea alba at this level (IAF-measurement).

MRI-scans (n = 452) The distance in mm was measured between the aorta and the linea alba at the level of the origin of the superior mesenteric artery (IAF-measurement).

Statistics Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp (IBM Corp. Released 2012). Spearman's rho correlation coefficients (r) were calculated to evaluate the relationship between variables; BMI vs. outcome, volumetric measurements vs. outcome (only in the CT-cohort) and IAF vs. outcome. Multivariable regression models were applied entering BMI and volumetric values in the CT-cohort versus BMI and IAF-measurements in the MRI-cohort. *P*-values <0.05 were considered statistically significant.

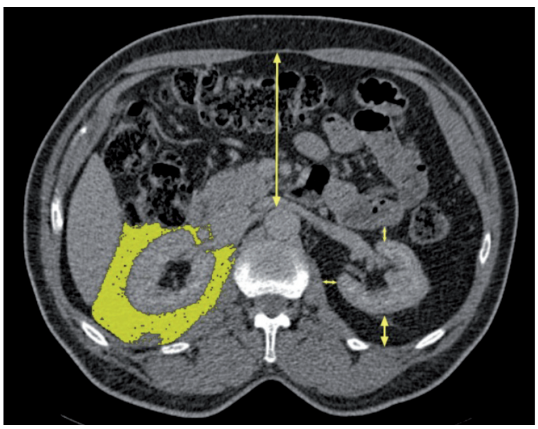

FIGURE 1. Perirenal volumetric measurements as indicated around the right kidney and IAF-measurement (from linea alba to the superior mesenteric artery).

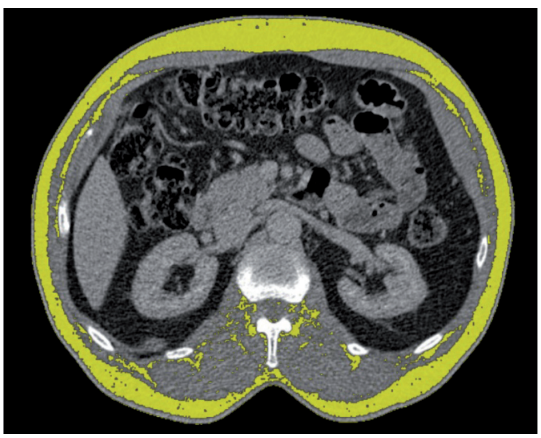

FIGURE 2. Volumetric measurement of total subcutaneous fat.

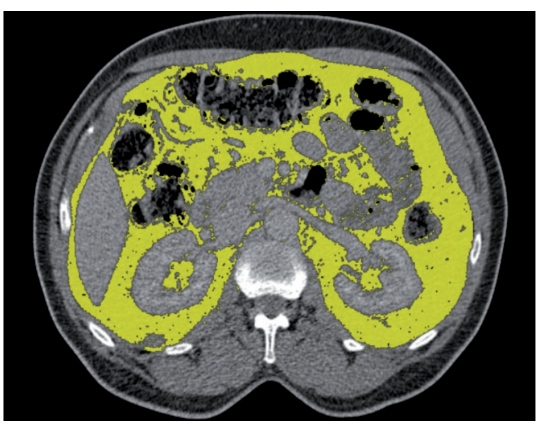

FIGURE 3. Volumetric measurement of total visceral fat.

RESULTS

Live kidney donors

Baseline characteristics

Of the 168 donors that had a preoperative CT, 76 (45.2%) were male and 92 (54.8%) were female. Donor nephrectomies in this group took place between 2005 and 2012. Median donor age was 52 years (range 20 – 83) with a median BMI of 25.2 kg/m^2 (range 17.2 – 46.9). Median operative time was 180 minutes (range 99 – 483) and median hospital stay was 3 (range 1 - 10) days.

Of the 452 donors that had a preoperative MRI, 197 (43.6%) were male and 255 (56.4%) were female. Donor nephrectomies of this group took place between 2003 and 2010. Median donor age was 52 (range 18 – 90) with a median BMI of 25.9 kg/m^2 (range 16.5 – 39.4). Mean operative time was 233 ± 65 minutes and median hospital stay was 3 (range 1 – 15) days (Table 1).

TABLE 1. Baseline characteristics.

	Total (n = 620)	**CT (n = 168)**	**MRI (n = 452)**
Male	273 (44.0%)	76 (45.2%)	197 (43.6%)
Age	52 (18 – 90)	52 (20 – 83)	52 (18 – 90)
BMI	25.6 (16.5 – 46.9)	25.2 (17.2 – 46.9)	25.9 (16.5 – 39.4)
Operative time (mins)	210 (99 – 478)	180 (99 – 438)	225 (100 – 478)
Length of stay (days)	3 (1 – 15)	3 (1 – 10)	3 (1 – 15)
Kidney side; left	56.2 %	62.9%	53.8%
WIT (mins)	4 (1 – 23)	4 (1 – 11)	5 (1 – 23)
Estimated blood loss (ml)	100 (0 – 3500)	75 (0 – 2000)	100 (0 – 3500)

CT-cohort (n = 168)

In the CT-cohort of 168 donors, the BMI only correlates with estimated blood loss and difference in serum creatinine (P=0.03 and P<0.001 respectively). As hypothesized, the volumetric measurements correlated with more outcome measures and had a stronger correlation. Operation duration (r=0.3, P<0.001), estimated blood loss (r=-0.1, P<0.001), difference in serum creatinine (r=0.4, P<0.001) and difference in eGFR (r=-0.3, P<0.01). The linear measurements of intra-abdominal fat correlated significantly with the same outcome measures with comparable coefficients except for difference in eGFR (Table 2A).

In multivariable analyses, BMI and the volumetric measurements were implemented in a regression model. Again, significant contribution is seen in operation duration (P=0.01), estimated blood loss (P<0.001), difference in serum creatinine (P<0.001) and difference in eGFR (P<0.01). In every outcome

parameter, the volumetric measurements show a significant contribution to the model whereas the BMI does not (Table 2B).

TABLE 2A. Correlation coefficients of BMI, perirenal fat, IAF-measurements and outcome measures (CT).

Outcome		BMI		Volumetric		IAF	
		correlation coefficient (r)	*P*	correlation coefficient (r)	*P*	correlation coefficient (r)	*P*
Operation duration		0.125	0.120	0.286	**<0.001**	0.180	**0.026**
Warm ischemia time		-0.100	0.206	0.066	0.404	-0.050	0.535
Estimated blood loss		0.177	**0.027**	0.306	**<0.001**	0.257	**0.001**
Length of stay		-0.040	0.606	-0.120	0.120	-0.127	0.104
Difference in serum creatinine		0.322	**<0.001**	0.406	**<0.001**	0.451	**<0.001**
Difference in eGFR		-0.093	0.320	-0.287	0.002	-0.173	0.065
Conversion (mean ± SD)	yes	24.77 ± 2.57	0.519	211.57 ± 150.82	0.442	102.55 ± 15.13	0.878
	no	25.89 ± 4.09		176.91 ± 132.45		101.51 ± 20.54	

TABLE 2B. Multivariable regression model, combining BMI and volumetric measurements.

Outcome	BMI + Volumetric			
	R^2	*P*	Estimate	*P*
Operation duration	0.058	0.011	BMI: -0.138 Volumetric: 0.109	0.912 **0.005**
Warm ischemia time	0.001	0.921	BMI: -0.058 Volumetric: 0.000	0.719 0.976
Estimated blood loss	0.143	**<0.001**	BMI: -1.131 Volumetric: 0.603	0.787 **<0.001**
Length of stay	0.001	0.893	BMI: -0.002 Volumetric: 0.000	0.953 0.682
Difference in serum creatinine	0.171	**<0.001**	BMI: 0.343 Volumetric: 0.032	0.207 **<0.001**
Difference in eGFR	0.090	**0.005**	BMI: 0.029 Volumetric: -0.019	0.881 **0.002**
Conversion	0.008	0.506	BMI: -0.004 Volumetric: 0.000	0.325 0.338

MRI-cohort (n = 452)

In the MRI-cohort of 452 donors, all outcome measures except warm ischemia time and difference in serum creatinine were significantly correlated with BMI. Operation duration (r = 0.157, *P*<0.001), estimated blood loss (r=0.155, *P*=0.002), length of stay (r=0.103, *P*=0.029) and difference in eGFR (r=-0.130, *P*=0.009). Remarkably, the IAF was significantly higher in the conversion group (*P*=0.009) (Table 3A).

In the multivariable analyses, the same significant correlations are seen, and furthermore, the IAF-measurements show a significant contribution to the conversion rate. In some of the outcome measures the IAF-measurements contribute significantly, in difference in eGFR, both BMI and IAF contribute and in length of stay, only the BMI contributes significantly (Table 3B).

TABLE 3A. Correlation of BMI and outcome measures + IAF-measurements and outcome measures (MRI).

Outcome		**BMI**		**IAF**	
		correlation coefficient (r)	***P***	**correlation coefficient (r)**	***P***
Operation duration		0.157	**0.001**	0.197	**<0.001**
Warm ischemia time		0.019	0.703	0.019	0.699
Estimated blood loss		0.155	**0.002**	0.257	**<0.001**
Length of stay		0.103	**0.029**	0.005	0.922
Difference in serum creatinine		0.076	0.126	0.290	**<0.001**
Difference in eGFR		-0.130	**0.009**	-0.151	**0.002**
Conversion (mean ± SD)	yes (n=18)	26.41 ± 2.90	0.486	87.73 ± 23.57	**0.009**
	no (n=434)	26.0 ± 3.81		73.0 ± 21.68	

TABLE 3B. Multivariable regression model, combining BMI and IAF-measurements.

Outcome	**BMI + IAF**			
	R^2	***P***	**Estimate**	***P***
Operation duration	0.040	**<0.001**	BMI: 0.910 IAF: 0.510	0.302 **0.001**
Warm ischemia time	0.003	0.582	BMI: 0.041 IAF: -0.002	0.308 0.807
Estimated blood loss	0.019	**0.021**	BMI: -0.496 IAF: 2.459	0.929 **0.011**
Length of stay	0.019	**0.014**	BMI: 0.056 IAF: 0.000	**0.007** 0.933
Difference in serum creatinine	0.002	0.681	BMI: -0.180 IAF: 0.133	0.816 0.388
Difference in eGFR	0.038	**<0.001**	BMI: -0.331 IAF: -0.061	**0.004** **0.029**
Conversion	0.018	**0.018**	BMI: -0.002 IAF: 0.001	0.426 **0.005**

Renal transplant recipients (n = 491)

Donor BMI and IAF-values were correlated with outcome of 491 renal transplant recipients. Interestingly, donor BMI only correlated significantly with WIT, estimated blood loss and DGF. Correlation coefficients were low in all outcome measures, and with increasing BMI, the incidence of DGF was lower. However, all significance was lost in the IAF-measurements, proving that both BMI as well as the amount of intra-abdominal fat of live kidney donors is not a good predictor for outcome in renal transplant recipients.
We were also interested whether recipient BMI was correlated with outcome of renal transplant recipients. As shown in Table 5, only regarding operation duration, warm ischemia time, estimated blood loss and difference in serum creatinine on day 1, significance was seen.

TABLE 4. Correlation coefficients of donor BMI and IAF-measurements (CT + MRI) with intra- and postoperative outcome of renal transplant recipients.

Outcome	**BMI**		**IAF**	
	correlation coefficient (r)	***P***	**correlation coefficient (r)**	***P***
Operation duration	-0.009	0.875	-0.038	0.517
Warm ischemia time	0.140	**0.002**	-0.033	0.480
Estimated blood loss	0.131	**0.007**	0.049	0.317
Length of stay	-0.009	0.845	-0.025	0.579
Difference in serum creatinine[a]	0.055	0.226	0.014	0.768
Difference in serum creatinine[b]	0.029	0.699	-0.125	0.093
DGF	-0.111	**0.014**	-0.022	0.623
PNF	0.049	0.275	0.040	0.384
Diuresis directly after reperfusion	-0.054	0.249	0.022	0.643
PCN insertion	-0.036	0.430	0.038	0.637
Complication rate	0.054	0.239	0.083	0.071
Thrombosis rate	0.038	0.409	0.007	0.881
Graft survival	-0.019	0.676	-0.015	0.745
Death	0.078	0.084	-0.011	0.814

a: difference of serum creatinine between the first day after surgery and preoperative values. b: difference of serum creatinine between year one postoperative and preoperative values.

DISCUSSION

Since there is currently a worldwide shift in the eligibility criteria for live kidney donation, useful tools for careful donor screening are warranted.[3] In the Netherlands, about 10% of the general population has a BMI above 30. Interestingly, in our total cohort, 13.4% had a BMI above 30 (11.3% in the CT-cohort and 14.2% in the MRI-cohort), nicely confirming aforementioned shift in accepting possible live kidney donors. The British guidelines recommend that otherwise healthy overweight individuals (BMI 25-30) may safely proceed to kidney donation. Moderately obese individuals (BMI 30-35) should undergo care-

TABLE 5. Correlation coefficients of recipient BMI with intra- and postoperative outcome of renal transplant recipients.

Outcome	Recipient BMI	
	correlation coefficient (r)	*P*
Operation duration	0.142	**0.016**
Warm ischemia time	0.191	**<0.001**
Estimated blood loss	0.183	**<0.001**
Difference in serum creatinine[a]	-0.101	**0.029**
Difference in serum creatinine[b]	-0.092	0.218
DGF	-0.016	0.734
PNF	0.025	0.586
Diuresis directly after reperfusion	-0.040	0.403
PCN insertion	0.023	0.619
Complication rate	0.151	**0.001**
Thrombosis rate	0.006	0.898
Graft survival	0.057	0.214
Death	0.068	0.138

a: difference of serum creatinine between the first day after surgery and preoperative values. b: difference of serum creatinine between year one postoperative and preoperative values.

ful preoperative evaluation to exclude cardiovascular, respiratory, and kidney disease. The guidelines also suggest that as data on the safety of kidney donation in the very obese (BMI >35) are limited, such individuals should be discouraged from donating.[15] However, as we already know from our previous meta-analysis, the BMI in itself might not be a useful parameter for selecting live kidney donors, we undertook this study to investigate whether other parameters might be sufficient to assess possible risks for a donor.[1] We have shown that in both univariable as in multivariable analyses the amount of perirenal fat has a strong correlation and is an independent risk factor in outcome of LDN.

One could argue how to proceed in the future regarding overweight or obese potential live kidney donors. As we now see, many transplant centers only score a donor's body composition using the BMI. However, in our opinion, one should not in- or exclude a donor based on BMI alone. Often, although a donor might have a high BMI, the excess weight is not centered around the abdomen, but more around the waist. In those cases, a donor would likely pose no surgical challenge. It should be noted however, that obesity often does not come alone, obese donors could have one or more comorbidities. The selection for donation by an obese potential donor should be a careful individualized process, where all possible comorbidities must be carefully interpreted. The most important factor is the pretransplant renal function and, obviously, the reserve capacity of the remaining kidney. The donors' health should always be prioritized, especially in this selective group, as data on long-term renal function of obese

donors are scarce. In addition, counselling should be provided to control weight, and appropriate medical follow-up should be maintained after donation.

Another consideration is the option of bariatric surgery prior to donation, in morbid obese potential donors (BMI > 40). If other conventional methods for losing weight with the help of a dietician are insufficient, this option could be considered. Moreover, consensus is that all individuals with morbid obesity (regardless of being considered as potential donor), are candidates to undergo bariatric surgery.[16]

Limitations

Although we have a fairly large cohort on which the analyses were performed, we have to acknowledge that results could change if the number of donors analysed was larger, specifically regarding the volumetrics performed on the CT-scans (n = 168). Furthermore, although the amount of perirenal fat has a better correlation with outcome after LDN than BMI, as stated above, transplant professionals have to be aware that a higher body weight is often accompanied by other comorbidities such as hypertension, hyperlipidaemia or even diabetes. Therefore, we underline that even if a donor with a high BMI has relatively low amounts of intra-abdominal or perirenal fat, careful consideration is warranted.

Concluding, in this large cohort of live kidney donors, we have confirmed that BMI alone is not the best predictor for outcome of LDN. Although the BMI correlates with some outcome of LDN, the amount of perirenal fat demonstrates a stronger correlation in even more outcome measures. Furthermore, the IAF-measurement shows the same correlation, both in the CT-cohort as in the MRI-cohort. Importantly, since the IAF is a linear measurement, no complex software is required. Therefore, we conclude that the measurement of intra-abdominal fat is a useful parameter in predicting peri- and postoperative outcome of LDN and should be included in the assessment of possible live kidney donors.

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Chapter 7

Body Mass Index and outcome in renal transplant recipients: A systematic review and meta-analysis

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ABSTRACT

Background Whether overweight or obese end stage renal disease (ESRD) patients are eligible for renal transplantation (RT) is often debated. The objective of this review and meta-analysis was to systematically investigate the outcome of low versus high BMI recipients after RT.

Methods Comprehensive searches were conducted in MEDLINE OvidSP, Web of Science, Google Scholar, Embase and CENTRAL (the Cochrane Library 2014, issue 8). We reviewed four major guidelines that are available regarding (potential) RT recipients. The methodology was in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and written based on the PRISMA statement. The quality assessment of studies was performed by using the GRADE tool. A meta-analysis was performed using Review Manager 5.3. Random-effects models were used.

Results After identifying 5,526 studies addressing this topic, 56 studies were included. We extracted data for 37 outcome measures (including data of more than 209,000 RT recipients), of which 26 could be meta-analyzed. The following outcome measures demonstrated significant differences in favour of low BMI (<30) recipients: mortality (RR=1.52), delayed graft function (RR=1.52), acute rejection (RR=1.17), 1-, 2-, and 3-year graft survival (RR=0.97, 0.95, and 0.97), 1-, 2-, and 3-year patient survival (RR=0.99, 0.99, and 0.99), wound infection and dehiscence (RR=3.13, and 4.85), NODAT (RR=2.24), length of hospital stay (2.31 days), operation duration (0.77 hours), hypertension (RR=1.35), and incisional hernia (RR=2.72). However, patient survival expressed in hazard ratios was in significant favour of high BMI recipients. Differences in other outcome parameters were not significant.

Conclusions Several of the pooled outcome measurements show significant benefits for 'low' BMI (<30) recipients. Therefore, we postulate that ESRD patients with a BMI >30 preferably should lose weight prior to RT. If this cannot be achieved with common measures, in morbidly obese RT candidates, bariatric surgery could be considered.

BACKGROUND

As the incidence of overweight and obesity rises globally, so does the number of end stage renal disease (ESRD) patients with obesity.[1] Renal transplantation (RT) is the preferred therapeutic option for ESRD, however, whether obese patients are eligible for RT is often debated due to the higher risk of complications.[2] Several guidelines state that obesity is not considered an absolute contra-indication, although patients with a body mass index (BMI) above 40 or 45 should not be considered for RT.[3,4] On the other hand, the guidelines state that if the transplant surgeon determines that the body composition of the potential RT recipient does not constitute an increased surgical risk, the patient should be suitable for RT. However, this does not take into account that it is not only the surgery itself that poses a possible risk. Equally important is the incidence of post-transplant complications in the obese recipient. Observational studies in the general population have demonstrated that obesity is an independent risk factor for chronic vascular disease.[5] Obesity is also associated with a number of risk factors for chronic vascular disease, including hypertension, dyslipidemia, and diabetes.[6] Of note, in general, the most important mortality and morbidity post-transplant is due to cardiovascular complications.[7]

Other possible complications that have previously been associated with a higher incidence in obese recipients are delayed graft function (DGF), impaired graft survival, longer hospital stay, higher costs, higher incidence of new onset of diabetes after transplantation (NODAT) and increased mortality.[8-11] Intuitively, all overweight potential recipients should lose weight prior to transplantation. Usually, dietary restriction is applied under the supervision of a dietician. However, in most cases, the desired result is not achieved, caused by several factors such as the need for dialysis three times a week, a low exercise tolerance, and comorbidities. In case of peritoneal dialysis, patients are known to increase in weight because the dialysate contains a high concentration of dextrose.[12] The body absorbs some of this dextrose during the dwell, which can lead to weight gain. Bariatric surgery (in case of morbid obesity or a BMI >35 with one or more comorbidities) could be considered, as it has proven to be successful in weight reduction in non-ESRD patients.[13,14] Few studies are available regarding bariatric surgery pre- or post-transplantation in (morbidly obese) ESRD-patients, however these all show promising results.[15-17] As has been recently published by Gill *et al.*,[18] the transplant community needs to realize that even obese RT recipients have a significant survival benefit from transplantation despite the reduced risk of death of obese dialysis patients.

Recently, Nicoletto *et al.*[19] carried out a systematic review and meta-analysis on the same topic, and conclude that obese patients have an increased risk for DGF. However, they only included 21 studies and did not include surgical outcome in these patients, which is an important topic in our opinion, as patients are frequently declined for RT because of the increased risk for surgical complications.
The aim of the present systematic review and meta-analysis is to give a more in-depth insight in (metabolic, survival, and surgical) outcome of low (<30) versus high (>30) BMI recipients after RT.

METHODS

All aspects of the Cochrane Handbook for Interventional Systematic Reviews were followed,[20] and the manuscript was written according to the PRISMA statement.[21]

Literature search strategy

Comprehensive searches were carried out in Embase, MEDLINE OvidSP, Web of Science, Google Scholar, CENTRAL (the Cochrane Library 2013, issue 5) and the Transplant Library. The search was performed for articles published until August 2014 relevant to outcome of kidney transplant recipients, both from a living or deceased donor. No language restriction was applied. Studies were included concerning patients that underwent RT, in which the recipients were divided according to BMI classification. As a cut-off value, a BMI of 30 was used to classify the included patients between 'low' (<30) and 'high' (> 30) BMI, according to the definitions of the World Health Organization.[22] Included outcome measures were: mortality (defined as death within follow-up of each study), patient survival at years 1, 2, and 3, graft survival at years 1, 2, and 3, primary non function, DGF (in 10 out of 30 studies defined as the need for dialysis within 7 days of transplantation), acute rejection, chronic rejection, graft loss, estimated glomerular filtration rate, operation duration, length of stay, lymphoceles, wound infection, incisional hernia, hematoma, wound dehiscence, surgical adverse events, NODAT, hypertension, and CMV infection. Search terms for each search-engine are provided as Additional file 1. Manual reference checks in included papers were performed to check for potentially missing studies.

Guideline Analysis

In addition to the literature search, we searched for guidelines regarding (potential) RT recipients in order to put the studies and their results in perspective. Specifically, sections about (pre-operative) overweight or obesity and RT suitability were reviewed.

Literature screening

Studies were evaluated for inclusion by two independent researchers (JAL, FJMFD) for relevance to the subject. Study selection was accomplished through several phases of screening. First, studies were excluded if they were one of the following: case-reports, letters, editorials, case-series, animal studies, or if the abstract revealed no relevance to the subject. For publications without abstract, the full text was acquired. In the next phase, inclusion required that studies described two or more groups of RT recipients divided based on their BMI and described relevant outcome measures.

Data extraction and critical appraisal

The level of evidence of each paper was established using the GRADE tool.[23] The GRADE approach defines the quality of a body of evidence by consideration of within study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias.

Statistical analysis

A meta-analysis was performed using Review Manager version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark). Random-effects models were used to account for possible clinical heterogeneity. Depending on the outcome, results were presented in forest plots with risk ratios or mean differences. Overall effects were determined using the Z-test; 95% CIs of these values were given and $P<0.05$ was considered statistically significant. Heterogeneity between studies was assessed by three methods. First, a Tau^2 test and a χ^2 test were performed for statistical heterogeneity, with a $P<0.1$ being considered statistically significant. Also, I^2 statistics were used to assess clinical heterogeneity, where an I^2 of 0% to 40% is considered as low heterogeneity, 30% to 60% as moderate heterogeneity, 50% to 90% as substantial heterogeneity, and 75% to 100% as considerable heterogeneity. Where studies reported on two or more high or low BMI groups, pooled mean estimates and standard deviations were calculated. Group means were weighted by the number of recipients in each study group. Funnel plot analysis was used to assess possible publication bias.

RESULTS

We included four major guidelines that are currently available regarding (potential) RT recipients: the Kidney Disease Improving Global Outcomes (KDIGO) 'Clinical Practice Guideline for the Care of the Kidney Transplant Recipient',[24] 'Assessment of the Potential Kidney Transplant Recipient' (5th edition, 2010) by the UK Renal Association,[25] the 'Guideline on Kidney Donor and Recipient Evaluation and Perioperative Care' by the European Renal Best Practice (ERBP) guideline body,[26] and Kidney Health Australia - Caring for Australasians with Renal Impairment (KHA-CARI): 'Recipient Assessment for Transplantation' and 'Obesity in renal transplantation'.[27]

The KDIGO guidelines state that, in RT recipients, obesity is associated with cardiovascular events and mortality. Furthermore, they mention that there is little reason to believe that weight reduction measures are not equally effective in obese potential RT recipients as in the general population. However, there is some indication that pharmacological and surgical management of obesity may be more likely to cause harm than in the general population. They recommend that additional research is needed to determine the effect of bariatric surgery on outcomes in RT recipients.

The UK Renal Association guideline states that obese patients (BMI>30) present technical difficulties and are at increased risk of peri-operative complications. They should be screened rigorously for cardiovascular disease and each case should be considered individually. Although obesity is not an absolute contra-indication to transplantation, individuals with a BMI>40 are less likely to benefit from RT.

The ERBP guideline states that the association between BMI and patient survival after RT is controversial based on current literature. Furthermore, it is recommended that RT candidates with a BMI>30 should lose weight prior to RT.

The KHA-CARI guidelines recommend that obesity alone should not preclude a patient from being considered for RT. Furthermore, they state that as a pre-transplant BMI>40 may not be associated with a survival advantage compared to remaining on dialysis, the suitability for transplant should be carefully assessed on an individual basis. Lastly, as patient and graft survival of obese transplant recipients may be mediated by comorbid factors, particularly cardiovascular, they recommend screening of obese transplant candidates for cardiovascular disease.

Literature search results

Out of 5,526 unique papers identified in the initial search, 56 studies were included. The PRISMA flow diagram for systematic reviews is presented in Figure 1. Data for 37 outcome measures were extracted (representing data of more than 209,000 recipients) of which 26 could be meta-analyzed. The characteristics of the included studies are presented in Table 1. The assessment of the quality of the included studies is presented in Figure 2.

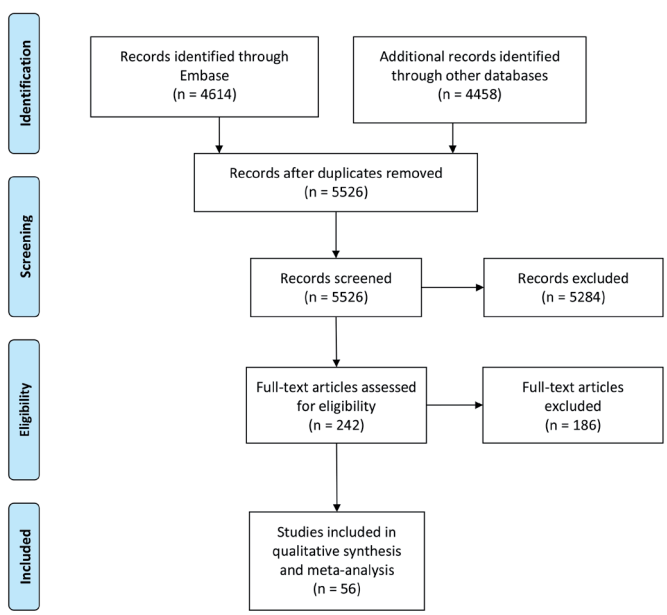

FIGURE 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart of the systematic literature search.

TABLE 1. Overview of the included studies in the systematic review.

Reference	Country	Year	BMI groups	n
Aalten [9]	The Netherlands	2006	<30	1,871
			≥30	196
Abou-Jaoude [28]	Lebanon	2010	<18.5	10
			18.5–24.9	62
			25.0–29.9	47
			≥30	16
Bardonnaud [29]	France	2012	<30	179
			≥30	21
Begov [30]	USA	2013	18–24.9	189
			25–29.9	169
			30–34.9	110
			≥35	78
Bennett [31]	USA	2011	<30	439
			30.1–34.9	109
			>35	89
Cannon [2]	USA	2013	<30	52,668
			30.0–34.9	15,010
			35.0–39.9	5,744
			≥40	1,561
Chang [32]	Australia	2007	<18.5	218
			18.5–24.9	2,719
			25.0–29.9	1,880
			≥30	867
Chow [33]	China	2006	<25	113
			≥25	37
Cockbain [34]	UK	2012	<18.5	731
			18.5–24.9	(combined)
			25.0–29.9	421
			≥30	197
Curran [35]	USA	2014	<20	100
			20–24.9	429
			25–29.9	364
			30–34.9	184
			≥35	74
Ditonno [36]	Italy	2011	<18.5	68
			18.6–24.9	310
			25.0–29.9	143
			30–34.9	32
			≤35	10
Dobbels [37]	Belgium	2008	<18.5	2,156
			18.6–24.9	18,345

TABLE 1. (Continued)

Reference	Country	Year	BMI groups	n
			25.0–29.9	15,040
			30–34.9	7,520
			≤35	3,401
Espejo [1]	Spain	2003	<30	40
			≥30	40
Farooq [38]	USA	2014	<36	27
			≥36	27
Furriel [39]	Portugal	2011	18.5–24.9	295
			25.0–29.9	127
			≥30	26
Gill [40]	USA	1993	<27	85
			>30	85
Gill [41]	USA	2013		Not reported
Gore [8]	USA	2005	<18.5	1,042
			18.5–24.9	12,089
			25.0–29.9	8,765
			30–34.9	3,891
			≥35	1,590
Grosso [42]	Italy	2012	<25	122
			25–30	190
			>30	64
Gusukuma [43]	Brazil	2011	<30	2,822
			30–34.9	185
			35–39.9	43
			≥40	4
Halme [44]	Finland	1995	20–25	235
			>30	47
Holley [45]	USA	1990	≤27 (male)	50
			≤25 (female)	
			≥30	46
Howard [46]	USA	2002	<25	457
			25–29.9	278
			≥30	98
Impedovo [47]	Italy	2012	<18.5	98
			18.6–24.9	428
			25–29.9	179
			≥30	58
Johnson [48]	Australia	2002	≤30	434
			>30	59
Kamali [49]	Iran	2010	<30	146

TABLE 1. (Continued)

Reference	Country	Year	BMI groups	n
			>30	34
Karabicak [50]	USA	2011	<20	74
			20–24.9	215
			25–29.9	193
			30–34.9	99
			≥35	61
Lynch [51]	USA	2009	<20	33
			20–30	491
			≥30	345
McGee [52]	USA	2008	<25	Not reported
			25–29	
			≥30	
Marcen [53]	Spain	2007	<18.5	63
			18.5–24.9	617
			25–29.9	255
			≥30	65
Marks [54]	USA	2004	≤28	224
			≥35	23
Massarweh [55]	USA	2005	<30	137
			≥30	56
Mehta [56]	USA	2007	<30	37
			≥30	16
Meier-Kriesche [10]	USA	1999	≤25	240
			>25	165
Modlin [57]	USA	1997	<27	127
			>30	127
Molnar [58]	USA	2011	≤19.9	Not reported
			20–21.99	
			22–24.99	
			25–29.99	
			30–34.99	
			≥35	
Moreira [59]	Brazil	2013	<18.5	31
			18.5–24.9	248
			25–29.9	120
			≥30	48
Papalia [60]	Italy	2010	18.5–25	110
			25–30	84
Patel [61]	USA	2011	<30	315
			≥30	160
Pieloch [62]	USA	2014	18.5–24.9	24,077

TABLE 1. (Continued)

Reference	Country	Year	BMI groups	n
			35–40	6,055
Pirsch [63]	USA	1995	<27.5	466
			27.5–30	59
			>30	59
Powers [64]	USA	2010	<25	34
			25–30	34
			>30	20
Rais-Jalali [65]	Iran	2005	<20	56
			20–24.9	86
			25–29.9	28
			≥30	12
Rajab [66]	USA	2007	<25	411
			25–29.9	416
			30–34.9	292
			35–39.9	106
			>40	80
Ravindra [67]	USA	2013	<25	Not reported
			25–29	
			30–34	
			≥35	
Schwarznau [68]	USA	2008	<30	56
			>30	25
Singh [69]	Canada	2005	≤30	35
			>30	33
Tang [70]	USA	2011	18–24.9	136
			25–29.9	116
			30–34.9	66
			<20	54
Tremblay [71]	USA	2014	20–24.9	32
			25–29.9	119
			30–34.9	149
			≥35	110
				57
Turner [4]	USA	2007	<30	753
			≥30	241
Walczak [72]	USA	2010	<30	61
			>30	46
Weissenbacher [73]	Austria	2012	<25	746
			>25	367
Wolyniec [74]	Poland	2011	<30	29
			≥30	29

TABLE 1. (Continued)

Reference	Country	Year	BMI groups	n
Yamamoto [75]	USA	2002	<30	28
			>30	28
Zaydfudim [76]	USA	2010	18.5–24.9	154
			25–29.9	192
			30–34.9	80
			≥35	38
Zrim [77]	Australia	2012	<18.5	10
			18.5–24.9	182
			25–29.9	194
			30–34.9	93
			≥35	29

Although the search could have identified randomized controlled trials, only observational studies were found, as randomized controlled trials addressing this topic does not seem to be feasible.

Survival outcome parameters

Mortality The number of deceased patients was studied in 16 studies including a total of 5,489 RT recipients.[10,31,33,39,40,42,45,46,48,50,55,57,59,65,72,75] The overall risk ratio was 1.52 (confidence interval (CI), 1.14-2.03; P=0.004, I^2=47%; P=0.02) for high BMI recipients (Figure 3). Five studies assessed the mortality rate in a regression model.[9,32,41,42,62] Overall, there were no significant differences with an overall hazard ratio of 1.01 (CI, 0.89-1.15; P=0.87, I^2=87%; P<0.01). Massarweh *et al.*[55] also expressed mortality in odds ratios; OR, 1.39 (CI, 0.43-4.49; P=0.58, I^2 not applicable).

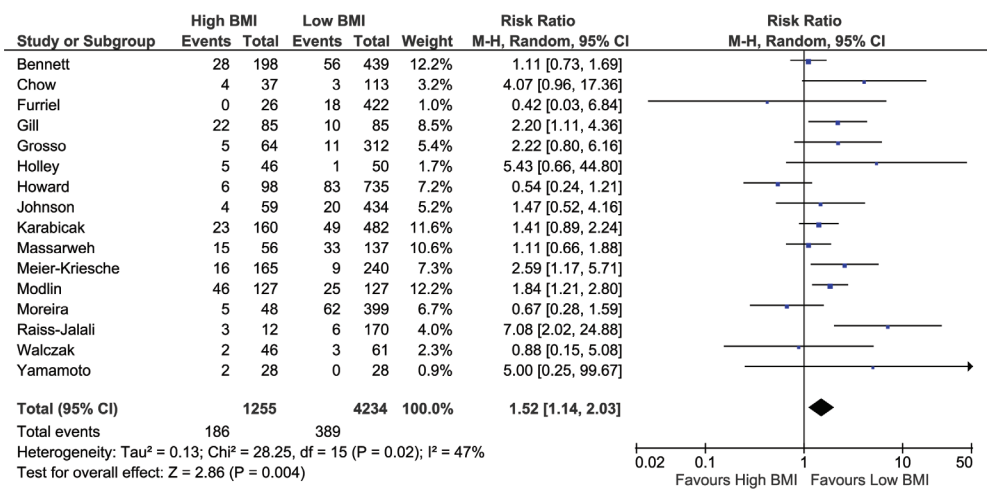

FIGURE 3. Forest plot of comparison: high versus low BMI recipients; outcome: mortality

Kidney transplantation in high versus low BMI recipients

Patient or population: high BMI recipients
Settings:
Intervention: Kidney Transplantation

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk Kidney Transplantation	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Mortality Follow-up: 20 years	**Study population**		**RR 1.52** (1.12 to 2.07)	4776 (13 studies)	⊕⊕⊖⊖ **low**[1]	
	85 per 1000	**130 per 1000** (96 to 177)				
	Moderate					
	46 per 1000	**70 per 1000** (52 to 95)				
Patient Survival 1 year Follow-up: 8.8 years	**Study population**		**RR 0.99** (0.99 to 1)	79553 (9 studies)	⊕⊕⊖⊖ **low**[1]	
	969 per 1000	**959 per 1000** (959 to 969)				
	Moderate					
	970 per 1000	**960 per 1000** (960 to 970)				
Patient Survival 2 years Follow-up: 2 years	**Study population**		**RR 0.99** (0.95 to 1.02)	585 (2 studies)	⊕⊕⊖⊖ **low**[1]	
	987 per 1000	**977 per 1000** (938 to 1000)				
	Moderate					
	990 per 1000	**980 per 1000** (940 to 1000)				
Patient Survival 3 years Follow-up: 8.8 years	**Study population**		**RR 0.99** (0.98 to 0.99)	76355 (5 studies)	⊕⊕⊖⊖ **low**[1]	
	925 per 1000	**916 per 1000** (907 to 916)				
	Moderate					
	925 per 1000	**916 per 1000** (907 to 916)				
Graft Survival 1 year Follow-up: 20 years	**Study population**		**RR 0.96** (0.94 to 0.98)	5858 (12 studies)	⊕⊕⊖⊖ **low**[1]	
	938 per 1000	**900 per 1000** (882 to 919)				
	Moderate					
	946 per 1000	**908 per 1000** (889 to 927)				
Graft Survival 2 years Follow-up: 20 years	**Study population**		**RR 0.95** (0.92 to 0.99)	735 (3 studies)	⊕⊕⊖⊖ **low**	
	968 per 1000	**920 per 1000** (891 to 958)				
	Moderate					
	966 per 1000	**918 per 1000** (889 to 956)				

Graft Survival 3 years Follow-up: 20 years	**Study population**	**RR 0.93** (0.89 to 0.97)	1583 (6 studies)	⊕⊕⊖⊖ **low**[1]
	889 per 1000	**827 per 1000** (792 to 863)		
	Moderate			
	917 per 1000	**853 per 1000** (816 to 889)		
PNF Follow-up: 7.9 years	**Study population**	**RR 2.53** (0.72 to 8.92)	1844 (3 studies)	⊕⊕⊖⊖ **low**[1]
	9 per 1000	**23 per 1000** (6 to 80)		
	Moderate			
	5 per 1000	**13 per 1000** (4 to 45)		
Delayed Graft Function Follow-up: 20 years	**Study population**	**RR 1.57** (1.35 to 1.83)	12358 (23 studies)	⊕⊕⊖⊖ **low**[1]
	187 per 1000	**293 per 1000** (252 to 341)		
	Moderate			
	147 per 1000	**231 per 1000** (198 to 269)		
Acute Rejection Follow-up: 20 years	**Study population**	**RR 1.22** (1.04 to 1.42)	9205 (19 studies)	⊕⊖⊖⊖ **very low**[1,2]
	216 per 1000	**263 per 1000** (224 to 306)		
	Moderate			
	171 per 1000	**209 per 1000** (178 to 243)		
Chronic Rejection Follow-up: 7.9 years	**Study population**	**OR 0.76** (0.15 to 3.84)	1281 (2 studies)	⊕⊖⊖⊖ **very low**[2]
	93 per 1000	**73 per 1000** (15 to 283)		
	Moderate			
	102 per 1000	**79 per 1000** (17 to 304)		
Graft Loss Follow-up: 8.8 years	**Study population**	**RR 1.5** (0.84 to 2.67)	925 (3 studies)	⊕⊕⊖⊖ **low**[1]
	88 per 1000	**132 per 1000** (74 to 235)		
	Moderate			
	107 per 1000	**160 per 1000** (90 to 286)		
eGFR 1 year Follow-up: 5 years	The mean egfr 1 year in the intervention groups was **7.53 higher** (3.17 lower to 18.24 higher)		1453 (3 studies)	⊕⊖⊖⊖ **very low**[2]
eGFR 3 years Follow-up: 20 years	The mean egfr 3 years in the intervention groups was **3.9 lower** (11.38 lower to 3.58 higher)		412 (2 studies)	⊕⊕⊖⊖ **low**
eGFR 5 years Follow-up: 5 years	The mean egfr 5 years in the intervention groups was **0.1 lower** (9.24 lower to 9.04 higher)		134 (1 study)	⊕⊕⊖⊖ **low**[1]

Operation Duration Follow-up: 6 years		The mean operation duration in the intervention groups was **0.3 higher** (0.27 to 0.33 higher)		493 (1 study)	⊕⊕⊖⊖ **low**
Length of Stay Follow-up: 14.2 years		The mean length of stay in the intervention groups was **2.3 higher** (1.04 to 3.55 higher)		4524 (9 studies)	⊕⊕⊖⊖ **low**
Wound Infection Follow-up: 8.8 years	**Study population**		**RR 3.99** (2.32 to 6.87)	2338 (9 studies)	⊕⊕⊕⊖ **moderate**[1,3]
	47 per 1000	**187 per 1000** (109 to 323)			
	Moderate				
	39 per 1000	**156 per 1000** (90 to 268)			
Hematoma Follow-up: 6 years	**Study population**		**RR 0.89** (0.34 to 2.34)	1041 (5 studies)	⊕⊕⊖⊖ **low**
	105 per 1000	**93 per 1000** (36 to 245)			
	Moderate				
	21 per 1000	**19 per 1000** (7 to 49)			
Lymphocele Follow-up: 5 years	**Study population**		**RR 2.32** (0.72 to 7.4)	375 (3 studies)	⊕⊖⊖⊖ **very low**[2]
	55 per 1000	**127 per 1000** (39 to 404)			
	Moderate				
	45 per 1000	**104 per 1000** (32 to 333)			
Wound dehiscence Follow-up: 6 years	**Study population**		**RR 5.12** (3.29 to 7.99)	3922 (5 studies)	⊕⊕⊕⊕ **high**[1,4]
	16 per 1000	**84 per 1000** (54 to 131)			
	Moderate				
	0 per 1000	**0 per 1000** (0 to 0)			
Incisional Hernia Follow-up: 4.4 years	**Study population**		**RR 2.72** (1.05 to 7.06)	261 (2 studies)	⊕⊕⊕⊖ **moderate**[1,3]
	41 per 1000	**111 per 1000** (43 to 287)			
	Moderate				
	36 per 1000	**98 per 1000** (38 to 254)			
Surgical Adverse Events Follow-up: 9.3 years	**Study population**		**RR 1.3** (1.05 to 1.62)	1712 (5 studies)	⊕⊕⊖⊖ **low**[1]
	213 per 1000	**277 per 1000** (224 to 345)			
	Moderate				
	232 per 1000	**302 per 1000** (244 to 376)			

NODAT Follow-up: 20 years	**Study population**		**RR 2.21** (1.44 to 3.37)	3398 (3 studies)	⊕⊕⊖⊖ **low**[2,3]
	155 per 1000	**343 per 1000** (223 to 522)			
	Moderate				
	73 per 1000	**161 per 1000** (105 to 246)			
Hypertension Follow-up: 5 years	**Study population**		**RR 1.35** (1.09 to 1.67)	194 (1 study)	⊕⊖⊖⊖ **very low**[5]
	545 per 1000	**736 per 1000** (595 to 911)			
	Moderate				
	546 per 1000	**737 per 1000** (595 to 912)			
CMV Infection Follow-up: 20 years	**Study population**		**RR 0.69** (0.2 to 2.37)	257 (2 studies)	⊕⊕⊖⊖ **low**
	75 per 1000	**52 per 1000** (15 to 179)			
	Moderate				
	72 per 1000	**50 per 1000** (14 to 171)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Symmetrical funnel plot
[2] Asymmetrical funnel plot
[3] More than 2 studies showing a RR of >2
[4] More than 2 studies showing a RR of >5
[5] Only one study available

FIGURE 2. Summary of findings table of extended criteria in live kidney donation generated by the GRADE tool.

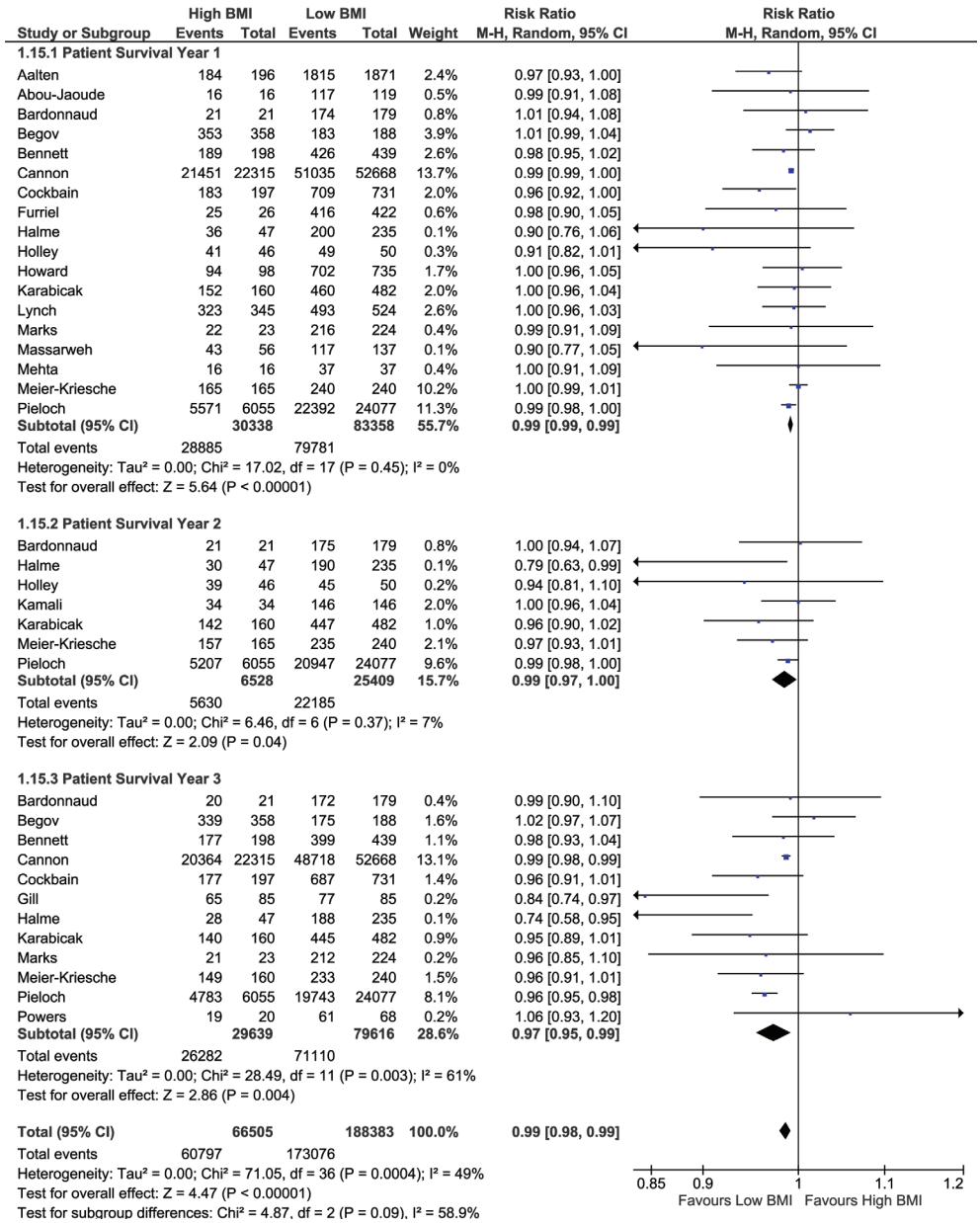

FIGURE 4. Forest plot of comparison: high versus low BMI recipients; outcome: patient survival at 1, 2 and 3 years.

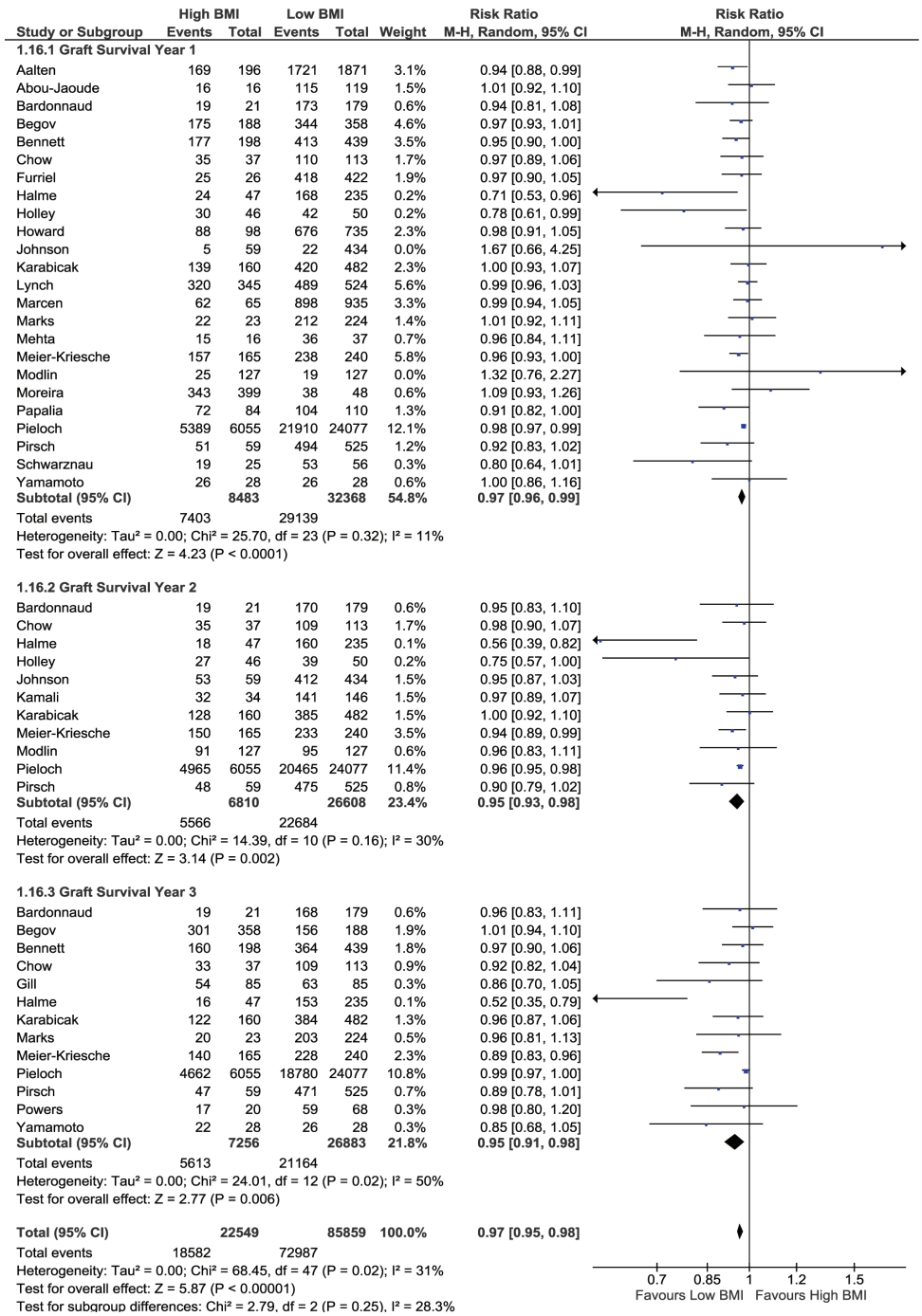

FIGURE 5. Forest plot of comparison: high versus low BMI recipients; outcome: graft survival at 1, 2, and 3 years and hazard ratio of graft survival.

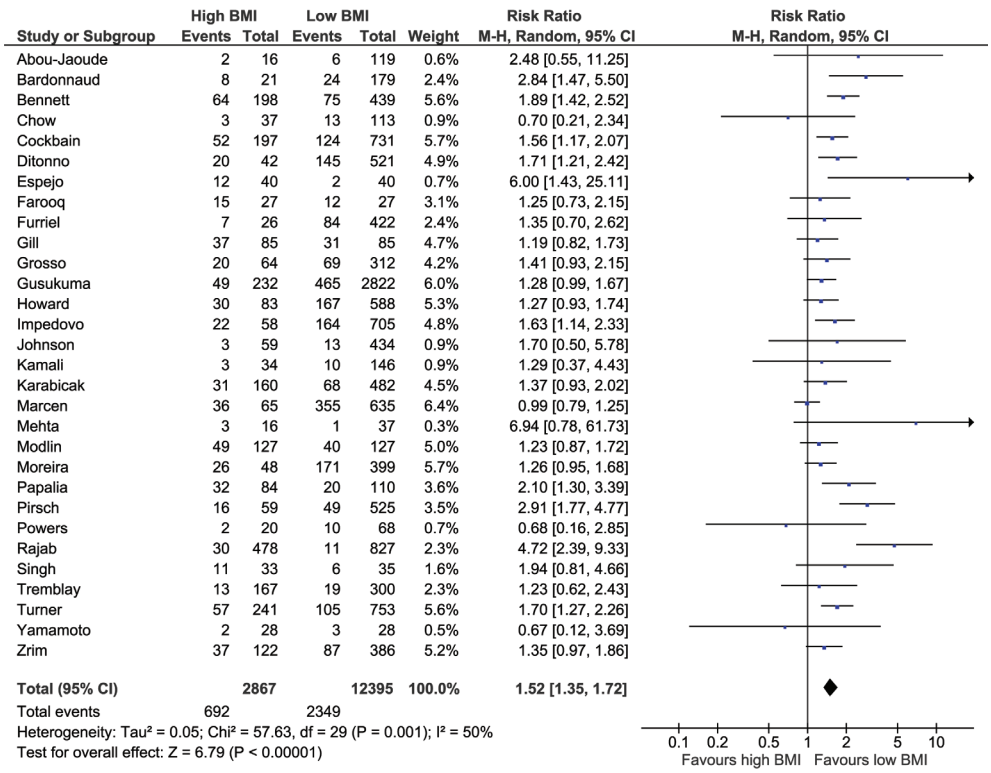

FIGURE 6. Forest plot of comparison: high versus low BMI recipients; outcome: delayed graft function.

Patient survival (1-, 2-, and 3-year) One-year patient survival was analysed in 18 studies and showed better survival for low BMI recipients (risk ratio (RR)=0.99, CI, 0.99-0.99; $P<0.001$, $I^2=0\%$; $P=0.45$).[2,9,10,28-31,34,39,44-46,50,51,54-56,62] At 2 years, seven studies showed a significant difference between recipient groups, again in favour of low BMI recipients (RR=0.99, CI, 0.97-1.00; $P=0.04$, $I^2=7\%$; $P=0.37$).[10,29,44,45,50,62,78] The 3-year patient survival was investigated in 12 studies, showing significant differences with a risk ratio of 0.97 (CI, 0.95-0.99; $P=0.004$, $I^2=61\%$; $P=0.003$; Figure 4).[2,10,29-31,34,40,44,50,54,62,64] Interestingly, the five studies that included BMI in regression analyses showed that a higher BMI is associated with a higher patient survival with an overall hazard ratio of 0.93 (CI, 0.89-0.97; $P<0.001$, $I^2=0\%$; $P=0.68$).[2,29,30,51,53] Grosso *et al.*[42] calculated an odds ratio of 27.98 (CI, 3.25-240.89; $P=0.002$, I^2 not applicable) in high BMI recipients.

Graft survival (1-, 2-, and 3-year) Twenty-four studies investigated 1-year graft survival and showed a better graft survival in recipients with a low BMI (RR=0.97, CI, 0.96-0.99; $P<0.001$, $I^2=11\%$; $P=0.32$).[9,10,28-31,33,39,44-46,48,50,51,53,54,56,57,59,60,62,63,68,75] Eleven studies assessed the 2-year graft survival.[10,29,33,44,45,48,50,57,62,63,78] The overall risk ratio was 0.95 (CI, 0.93-0.98; $P=0.002$, I^2 30%; $P=0.16$). The 13 studies that analysed 3-year graft survival showed an overall risk ratio of 0.95 (CI, 0.91-0.98; $P= 0.006$, $I^2=50\%$; $P= 0.02$).[10,29-31,33,40,44,50,54,62-64,75] In each year studied, graft survival was in favour of low BMI recipients (Figure 5). Seven studies included BMI

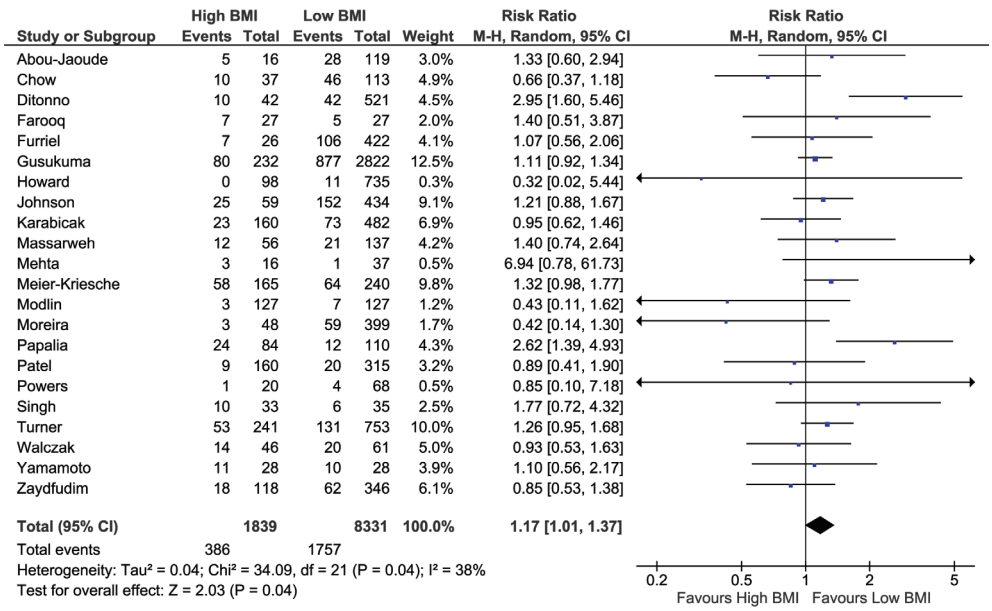

FIGURE 7. Forest plot of comparison: high versus low BMI recipients; outcome: acute rejection.

as a parameter in regression analyses showing no significant relation between BMI and graft survival. The overall hazard ratio was 1.00 (CI, 0.96-1.04; *P*=0.98, I^2=54%; *P*=0.04).[2,9,29,30,48,52,53] Grosso *et al.*[42] calculated an odds ratio (OR=0.98, CI, 0.13-7.39; *P*=0.98, I^2 not applicable).

Kidney function outcome parameters

Delayed Graft Function The incidence of DGF was assessed in 30 studies encompassing a total of 15,262 recipients.[1,4,28,29,31,33,34,36,38-40,42,43,46-48,50,53,56,57,59,60,63,64,66,69,71,75,77,78] The overall risk ratio was 1.52 (CI, 1.35-1.72; *P*<0.001, I^2=50%; *P*=0.001; Figure 6). Six studies assessed DGF in odds ratios ORs using a BMI of 30 as cut-off value.[2,8,32,35,58,73] The overall OR when pooling these studies was 1.38 (CI, 1.20-1.59; *P*<0.001, I^2=92%; *P*<0.01). The pooled OR when using a BMI of 35 as a cut-off was 1.96 (CI, 1.69-2.28; *P*<0.001, I^2=32%; *P*=0.23).[8,35,58]

Acute rejection The incidence of acute rejection was investigated in 22 studies.[4,10,28,33,36,38,39,43,46,48,50,55-57,59-61,64,69,72,75,76] Twelve studies showed a lower risk ratio on acute rejection in low BMI recipients. The overall risk ratio, including 10,170 recipients, was 1.17 (CI, 1.01-1.37; *P*=0.04, I^2=38%; *P*=0.04; Figure 7). Gore *et al.*[8] assessed the incidence of acute rejection in OR as 1.19 (CI, 1.11-1.28; *P*<0.001, I^2 not applicable).

Other outcome parameters showing no significant differences in kidney function outcome parameters are outlined in Table 2.

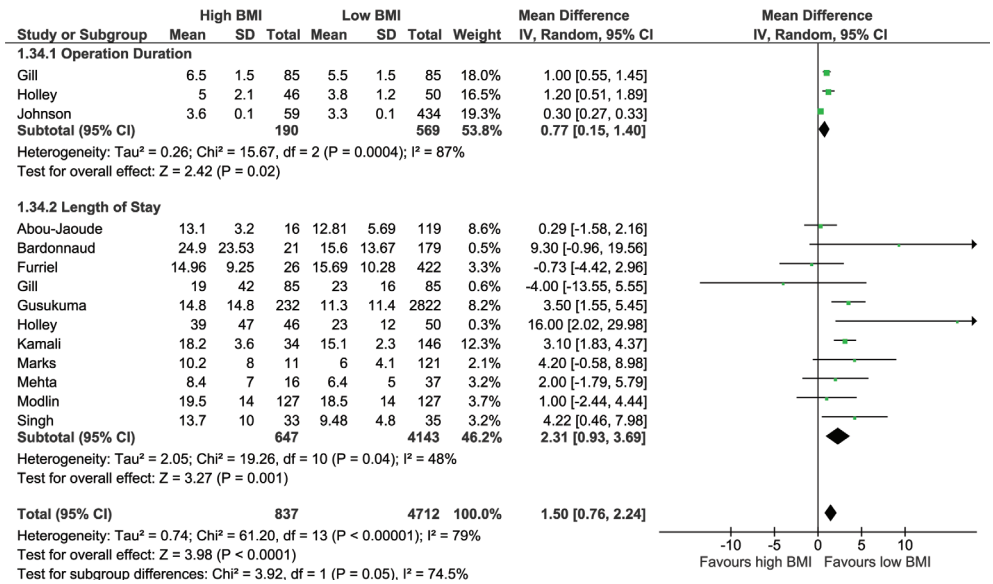

FIGURE 8. Forest plot of comparison: high versus low BMI recipients; outcome: operation duration and length of stay.

Surgical outcome parameters

Operation Duration Only three studies investigated the operation duration in low versus high BMI recipients, showing a mean difference of 0.77 hours (CI, 0.15-1.40), with a statistically significant difference (P=0.02, I^2=87%; P<0.01; Figure 8).[40,45,48]

Length of Stay The length of hospital stay was assessed in 11 studies.[28,29,39,40,43,45,54,56,57,69,78] All studies but two showed a mean length of stay in favour of low BMI recipients.[39,40] The overall mean difference was 2.31 days (CI, 0.93-3.69; P=0.001, I^2=48%, P=0.04; Figure 8).

Wound infection The incidence of wound infections was studied in 13 studies with a total of 4,504 recipients.[31,40,45,48,51,54-56,59,61,63,69,72,78] The overall risk ratio of this outcome was 3.13 (CI, 2.08-4.71; P<0.001, I^2=65%; P<0.01; Figure 9).

Incisional hernia Two studies assessed the incidence of incisional hernias.[55,69] The overall risk ratio was 2.72 (CI, 1.05-7.06; P=0.04, I^2=0%; P=0.82; Figure 9).

Wound dehiscence Six studies reported the incidence of wound dehiscence including 3,922 recipients.[29,43,48,51,69,72] The overall risk ratio was 4.85 (CI, 3.25-7.25; P<0.001, I^2=0%; P=0.75; Figure 10).

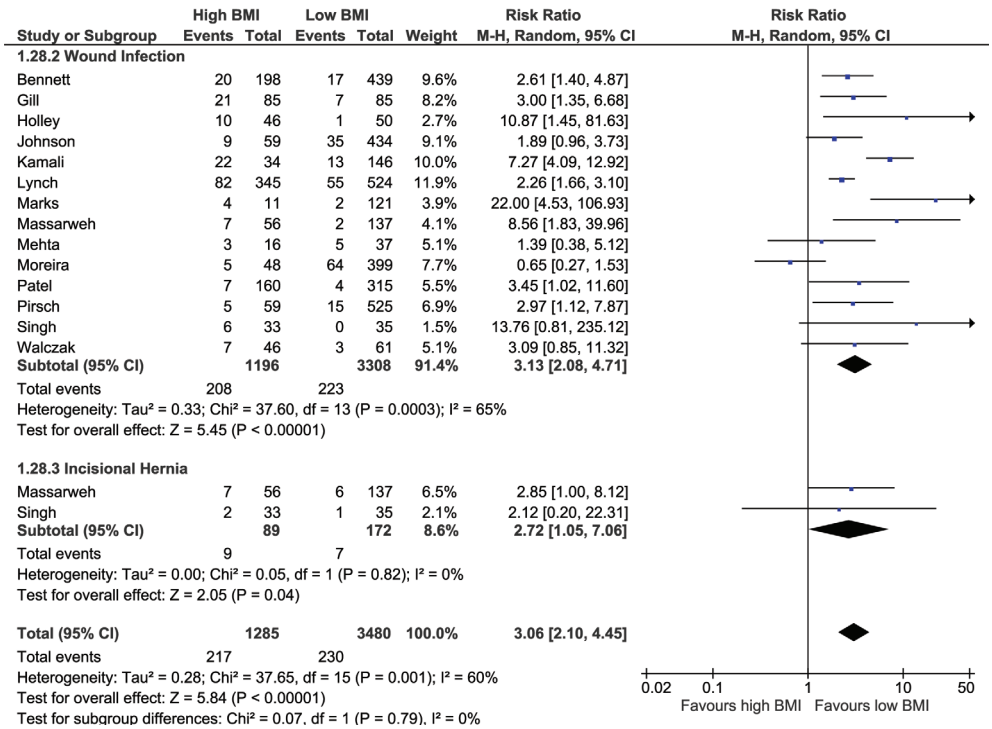

FIGURE 9. Forest plot of comparison: high versus low BMI recipients; outcome: wound infection and incisional hernia.

Surgical adverse events Five studies investigated surgical adverse events, such as urologic, vascular, and haemorrhagic complications.[28,36,39,74,77] The overall risk ratio was 1.30 (CI, 1.05-1.62; *P*=0.02, I^2=0%; *P*=0.65; Figure 10).

Other outcome parameters showing no significant differences in surgical outcome parameters are outlined in Table 3.

Metabolic outcome parameters

NODAT

Six studies including 4,111 recipients investigated the incidence of new onset diabetes after transplantation.[33,40,43,45,59,60] Overall, a risk ratio of 2.24 (CI, 1.46-3.45; *P*<0.001, I^2=53%; *P*=0.06) was found.

Hypertension Only one study assessed the incidence of hypertension in different BMI groups including 194 patients.[60] High BMI recipients had a higher risk on hypertension with a risk ratio of 1.35 (CI, 1.09-1.67; *P*=0.005, I^2 not applicable).

Other outcome parameters

Cytomegalovirus (CMV) infection The incidence of CMV infection was addressed in two studies.[33,72] Overall, the risk ratio was 0.69 (CI, 0.20-2.37; *P*=0.56, I^2=14%; *P*=0.28) in favour of low BMI recipients.

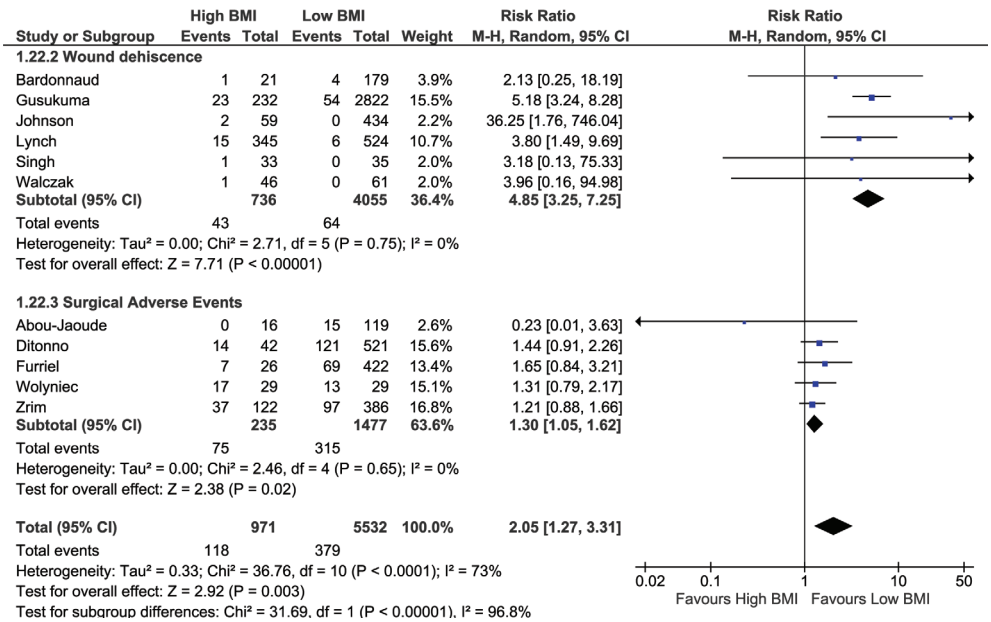

FIGURE 10. Forest plot of comparison: high versus low BMI recipients; outcome: wound dehiscence and surgical adverse events.

TABLE 2. Outcome parameters with no significant differences.

Outcome parameter	Studies	RR (CI)	*P*-value
Primary non function	3 [36,39,46]	2.53 (0.72-8.92)	0.15
Chronic rejection	2 [39,46]	0.18-3.54	0.76
Graft loss	5 [42,48,51,59,75]	1.14 (0.87-1.50)	0.34
		Mean difference (CI)	
eGFR year 1	3 [4,28,70]	7.53 mL/min (-3.17-18.24)	0.17
eGFR year 3	2 [33,70]	-3.90 mL/min (-11.38-3.58)	0.31
eGFR year 5	1 [70]	-0.10 mL/min (-0.24-9.04)	0.98

eGFR, Estimated glomerular filtration rate; RR, Risk ratio; CI, Confidence interval

DISCUSSION

With this meta-analysis, we aimed to determine whether guidelines or policy should be revised with respect to suitability for RT of overweight and obese (potential) recipients, since this is often debated. There are several central questions behind this need for additional insight. Should obese ESRD-patients

TABLE 3. Outcome parameters with no significant differences.

Outcome parameter	Studies	RR (CI)	*P*-value
Lymphoceles	4 [29,40,69,72]	1.74 (0.74-4.11)	0.20
Hematoma	5 [48,55,69,72,78]	0.89 (0.34-2.34)	0.82

RR, Risk ratio; CI, Confidence interval.

be transplanted at all? Are we and are these patients aware of all possible risks? Should we emphasize the need for weight loss, or even advise bariatric surgery before RT, and to whom?

The worldwide prevalence of obesity is rising, leading to an increasing number of patients with cardiovascular comorbidity, diabetes (metabolic syndrome) and, consequently, ESRD.[79-81] As RT is the golden standard in treating these patients, a good understanding of the consequences of transplanting overweight and obese ESRD-patients is needed. Several reviews have been written regarding this topic.[82-93] The KDIGO-guidelines state that observational studies report an association between obesity and mortality in RT recipients. The present study is the first meta-analysis investigating several (metabolic, survival, and surgical) outcome measures, and pooling data from a large number of studies (n = 56, including over 209,000 recipients).

Nicoletto *et al.*[19] recently published a systematic review and meta-analysis regarding this very subject. Their main finding was that recipient obesity is associated with an increased rate of DGF and that there was no association between obesity and acute rejection. One of the limitations of their study is that they included only 21 studies, whereas we included 56 publications. This could be explained by the fact that fewer databases have been searched by the authors (MEDLINE, EMBASE, and the Cochrane Library) than we did (Web of Science, Google Scholar, and the Transplant Library). Furthermore, the authors did not describe if any study was excluded based on the quality assessment of the Newcastle-Ottawa Quality Assessment Scale or the GRADE tool. Interestingly, the authors observed that studies published after 2003 show no differences in survival between BMI groups. Although they state that 2003 was used as a cut-off because of the fact that included patients were transplanted before 2000, they do not provide an explanation as to why obesity would pose a problem before 2000. In our opinion, other factors may contribute to this result, such as the fact that live kidney donation has increased over the years, providing better quality grafts resulting in increased graft and, thus, patient survival. Moreover, they did not analyse surgical outcome measures as wound infection and dehiscence. In our opinion these are important outcomes that should also be included in the informed consent procedure for the recipients. Finally, we have included a meta-analysis of hazard ratios of graft and patient survival in the included studies, showing more clearly that the BMI itself may not be the cause of worse outcome in RT recipients but rather other comorbidities associated with obesity such as diabetes or (cardio-)vascular disease. Perhaps different lifestyle recommendations should be provided to patients who remain on dialysis versus those who will be transplanted.[94]

Our results clearly show that, in recipients with a higher BMI, graft and patient survival are worse, at least up to 3 years after transplantation. Interestingly, in regression analyses, regarding patient survival, having a higher BMI seems to be associated with a higher patient survival, and regarding graft survival there appears to be no significant relation with the BMI. This could be explained by the 'obesity paradox', an interesting phenomenon that has been described for haemodialysis patients,[93] suggesting that patients on haemodialysis with a higher BMI tend to have an improved survival benefit. However, the improved survival benefit is associated with higher costs, more complications, and worse outcome after transplantation.[95] On the other hand, and perhaps most importantly, obese RT recipients still demonstrate significant survival benefit from transplantation compared to dialysis.[18]

The kidney function outcome parameters show that the incidence of DGF and acute rejection is higher in high BMI recipients. A possible explanation is that the operation duration is longer in recipients with a higher BMI, which in itself is associated with higher DGF-rates.[96] The increased incidence of acute rejection might be explained by the fact that obesity is linked to inflammation and modified immune responses, potentially impacting allorecognition and alloimmunity.[97] Another possibility is the increased finding of (not clinically relevant) rejection because of the higher incidence of biopsies in case of DGF.

Regarding the metabolic outcome parameters, increasing BMI shows a significant correlation with the development of NODAT and hypertension, which is not surprising, knowing that overweight and obesity are common risk factors for developing these comorbidities.[92,98]

All surgical outcome measures are significantly in favour of recipients with a low BMI, with exception of the incidence of hematoma and lymphoceles. A possible explanation could be that the latter two complications are not necessarily influenced by overweight or body composition, in contrast to wound dehiscence or hernias.[99,100]

Although a large part of our systematic review concerns long-term outcome measures, we should bear in mind that the perioperative (surgical) outcome measures are of great importance. Many RT candidates with a high BMI are declined because the concern of possible surgical difficulties and inherent complications. As confirmed by the results of the meta-analysis, this concern is justified. Therefore, high BMI RT candidates should be referred to tertiary referral centers to centralise knowledge about and experience with this patient category, especially on a transplant surgical level. Additionally, it is another motivator to encourage RT candidates to lose weight prior to transplantation, ideally several years before the operation. Nephrologists can play a crucial and proactive role in this process.

In summary, we conclude that obesity prior to RT leads to impaired outcome after RT. Losing weight prior to transplantation might be of great importance, although it is unclear whether this is advanta-

geous for ESRD patients who remain dependent on dialysis.[101] However, one should bear in mind that, even if sufficient weight loss cannot be achieved before transplantation, transplantation still leads to enormous advantages in terms of survival, health, and quality of life.[18] We have recently performed a study showing that patients who are deemed unsuitable for RT because of high BMI in one center have excellent outcome when transplanted in a tertiary high-volume center (Glijn *et al.*, manuscript in preparation). For overweight or obese recipients that will be transplanted, conventional methods to lose weight, such as dietary advice, might not lead to the desired (or sufficient) effect.[16,46,102] Even though some weight loss might be achieved, after transplantation, the weight is often regained, possibly caused by the metabolic changes that may result in better nutrient absorption and/or reduced energy expenditure with improved renal function after transplantation. Furthermore, the increased quality of life may lead to a larger food intake.[94,103]

Another, more effective, method to lose weight prior to or post-transplantation is bariatric surgery. Some studies have already been performed showing promising results.[15-17,104-107] Furthermore, it is already stated by several guidelines that any person with a BMI above 40, or a BMI higher than 35 with comorbidities, should be advised to undergo bariatric surgery,[108-110] since it has proven to resolve obesity-related comorbidities like diabetes, hypertension, sleep apnoea, and asthma and reduces mortality rates. An issue of concern, however, is whether an ESRD-patient is fit enough to undergo a risk reducing operation with the risk of complications in itself. In general, the complication and mortality rates after bariatric surgery have declined greatly over the years to about 0.3%.[111] A few studies on bariatric surgery in ESRD-patients show low complication and 90-day mortality rates close to 0%.[15,16,112-114] This is important to acknowledge because survival of patients on dialysis is far worse compared to the survival after RT.[18] Therefore, every possible RT candidate should be carefully assessed to see if possible complications of bariatric surgery, although being very low, would not pose a risk for the transplantation. In our opinion, every obese donor should be informed about this possibility, being aware of possible risks. A clinical trial is ongoing to investigate whether bariatric surgery before RT has benefits (ClinicalTrials.gov, number NCT01913392).

Limitations

It has to be acknowledged that a systematic review and meta-analysis can only be as good as the quality of the included studies. Potentially, several types of bias have been introduced in this analysis. The individual studies are prone to sampling bias because of the fact that they are observational studies. It is possible that, due to publication bias, the results have become skewed. However, based on funnel plot analyses (data not shown), we can safely state that publication bias is minimal. Another limitation is that not all studies have clearly specified the definition of certain outcome measures. For example, not all studies mention whether or not cases of acute rejection are, in fact, biopsy proven or the used definition of DGF. This may introduce bias in the analyses leading to heterogeneity. Moreover, only a few studies defined whether the transplanted kidneys were from live or deceased donors (donation after

circulatory death or donation after brain death), which is a confounding factor in the pooled analysis of DGF. It would be interesting to have this specific information, to see whether the hypothesis that high BMI recipients have better outcome when receiving a kidney from a living donor or a standard criteria 'donation after brain death' donor kidney can be confirmed. In line of this limitation, also the 'pre-transplant' status of a recipient is of importance; whether he or she was transplanted pre-emptively or was on haemo- or peritoneal dialysis prior to transplantation has an impact on the outcome after RT. It would be interesting if future studies would include other parameters that take into account the fat distribution of a recipient, as the BMI does not; for example, the waist circumference or hip-waist-ratio.[115] It could be that outcome would change if these parameters were correlated to outcome of RT recipients.

CONCLUSIONS

Based on our results, we make the following recommendations:

- RT candidates should not be excluded for transplantation on the basis of BMI alone.
- High BMI renal transplant candidates should be referred to high-volume/tertiary referral centers in order to keep knowledge about these category of patients centralized.
- Informed consent procedures for obese RT candidates should include the risk profiles associated with obesity and RT outcome.
- Both patients and clinicians should be aware of the importance of weight loss prior to transplantation.
- (Morbidly) obese RT candidates should be informed about all possible weight reduction methods, ranging from dietary restriction under supervision of a dietician to the option of bariatric surgery.
    - Obese RT candidates with a BMI between 30 and 35 should be referred to conventional methods of weight reduction, with help of a dietician.
    - Obese RT candidates with a BMI >35 and comorbidities or a BMI >40 should be referred for bariatric surgery, based on bariatric guidelines. Based on our experience, this could pose some difficulties for dialysis patients because of the required diet prior to bariatric surgery and age limits for bariatric surgery. Some bariatric centers have a maximum age limit of 60 for bariatric surgery. However, a large part of ESRD patients is over 60 years old. For these reasons, in our opinion, ESRD patients with morbid obesity cannot be compared to 'regular' morbid obese individuals.
- Ideally, in high BMI RT candidates, the process of weight reduction should be initiated several years before RT to ensure an adequate time period for remedial measures to become effective.
- Despite the poorer outcome of RT in these patients, the survival benefit of RT over dialysis needs to be emphasized. Therefore, we need to maximize our efforts for obese ESRD patients to get access to RT, and develop strategies to reduce the risks associated with RT in this patient category.
- Innovations in surgical techniques should be stimulated. For example, robot-assisted techniques for implantation could be promising for this specific patient category.[116]

ABBREVIATIONS

BMI, Body mass index; CI, Confidence interval; CMV, Cytomegalovirus; ESRD, End-stage renal disease; GRADE, Grades of Recommendation, Assessment, Development and Evaluation; KDIGO, Kidney Disease Improving Global Outcomes; NODAT, New onset diabetes after transplantation; OR, Odds ratio; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RR, Risk ratio; RT, Renal transplantation

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

JAL participated in the design of the study, evaluated studies for inclusion, performed the statistical analysis and data interpretation, and wrote the manuscript. MGHB participated in the design of the study, data interpretation, and helped to draft the manuscript. JNMIJ participated in the design and coordination of the study and helped to draft the manuscript. FJMFD conceived the study idea, participated in the design of the study, evaluated studies for inclusion, and helped to draft and supervised the writing of the manuscript. All authors read and approved the final manuscript.

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Chapter 8

Complex vascular anatomy should not be a contraindication for live kidney donation and transplantation

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ABSTRACT

Background Whether vascular multiplicity in live kidney donors should be considered as relative contraindication and 'extended donor criterion' is still under debate, as around 10% of the European centers only accept donors with singular anatomy.

Methods From 2006 to 2013, data from all live kidney donors (n=951) was collected, and retrospectively reviewed. Vascular anatomy as imaged by MRA, CTA, or other modalities was compared with intraoperative findings. Furthermore, the influence of vascular multiplicity on outcome of donors and respective recipients was studied.

Results In 237 donors, vascular multiplicity was present, 58.4% of them had bilateral multiplicity. CTA had higher accuracy levels compared with MRA regarding renal vascular anatomy assessment in this cohort. Regarding outcome of live donors with vascular multiplicity, warm ischemia time (WIT) and skin-to-skin time were significantly longer if arterial multiplicity (AM) was present (5.1 vs. 4.0 mins and 202 vs. 178 mins). Skin-to-skin time was significantly longer and complication rate (Clavien-Dindo grade I) was higher in donors with venous multiplicity (VM) (203 vs. 180 mins and 17.2% vs. 8.4%). Analysis of renal transplant outcome in recipients showed a significantly increased WIT (30 vs. 26.7 minutes), higher rate of DGF (13.9% vs. 6.9%) and lower rate of BPAR (6.9% vs. 13.9%) in patients receiving a donor kidney with AM compared with donor kidneys with singular anatomy. Most importantly, recipients had no impaired graft- and patient survival.

Conclusion CTA proves to be superior to MRA regarding correct preoperative anatomical imaging of a live kidney donor. Although significant differences were found in WIT and skin-to-skin time, we conclude that vascular multiplicity should not be considered as a contraindication to donation, since it has little impact on clinical outcome in the donor. Furthermore, renal transplant recipients receiving a donor kidney with multiple arteries or veins have excellent outcome.

INTRODUCTION

Live kidney donation has become increasingly important over the years in the field of renal transplantation (RT) and accounts for more than 55-60% of RT in The Netherlands.[1] Careful donor selection is essential to ensure donor safety. Due to the persistent donor organ shortage and increasing incidence of end-stage renal disease (ESRD),[2] there is a worldwide trend in accepting so called extended criteria live kidney donors (i.e., obese donors, older donors, or donors with hypertension).[3] Vascular multiplicity in live kidney donors is considered another extended criterion, because of the premise that it is associated with higher (surgical) complication rates in the recipient.[4-6] However, kidneys with multiple arteries and/or veins are common in kidney donors (between 18% and 20%),[7,8] and because of the donor shortage, it is likely that the acceptance of these kidneys for donation and transplantation will further increase over the years. Available literature suggest that outcome in donors with vascular multiplicity is excellent.[9,10] In 2008, Kok *et al*. investigated the live kidney donor cohort in our center from 2001 until 2005 regarding vascular multiplicity, showing that despite an increased warm ischemia time, operation time and increased blood loss in donors with multiple renal arteries, arterial multiplicity (AM) does not seem to be a contraindication for donation.[11] They reported, however, an increased incidence of urological complications after RT in donors with AM. During the timespan of the analysed cohort, predominantly magnetic resonance imaging (MRA) and digital subtraction angiography (DSA) were used as screening modalities for live kidney donors. Therefore, venous anatomy was not included in analyses, because renal veins are not visible with DSA. Since that time, our live kidney donation program has increased significantly, to the largest program in Europe with regular tertiary referrals, resulting in the inclusion of more extended criteria live kidney donors with excellent results.

According to current evidence and guidelines, single renal vascular anatomy is preferred in living kidney donors, although arterial or venous multiplicity (VM) should not be considered as an absolute contraindication for live kidney donation.[12-19] However, in most centers, renal vascular anatomy is one of the dominant factors in determining which kidney should be procured. In general, the kidney with the most straightforward vascular anatomy (ideally one artery, one vein) is chosen.

At the start of our program in the early 90's, radiographic angiography was used for preoperative donor anatomy assessment. After several years, MRA became the gold standard, followed by computed tomography (CT) from 2010 onwards.[20-22] In addition to increased accuracy of CTA compared with MRA, CTA offers other advantages as well.[20] Motion and partial volume artefacts are much less prevalent using CTA. Using MRA, these artifacts can, dependent on slice thickness, lead to an irregularly shaped appearance of the artery, which may cause false positive diagnosis of fibromuscular dysplasia.[23,24]

Recently, Fuller stated two principles regarding this issue in live donor nephrectomy:[25] First, 'do not harm the donor' and second; 'make optimal use of available living donors to overcome organ shortage. It may no longer seem acceptable to exclude otherwise suitable living donors only on grounds of technical obstacles'. In light of these remarks, and since in most centers still single renal vascular anatomy is preferred,[3] we decided to further study the influence of vascular multiplicity on outcome for live kidney donors and their recipients in our cohort. Furthermore, as CTA has been considered as gold standard in

assessing live kidney donors for several years, we also investigated the (dis)advantages of the imaging technique in light of vascular multiplicity.

We recently published a systematic review regarding extended donor criteria, including vascular multiplicity. Based on the included guidelines and available literature, it is concluded that vascular multiplicity (in particular, AM up to 3 renal arteries) should not be considered a contraindication for live kidney donation.[3]

In light of this review, we decided to investigate our cohort from 2006 until 2013, including nearly 1000 living kidney donors, aiming to get a deeper insight in the shift in acceptance of donors with vascular multiplicity, their potentially increased risk for complications in the donor and the RT recipient.

METHODS

From January 1st 2006 to December 31st 2013, data of all live kidney donors and renal transplantations (n=951) was collected and retrospectively reviewed. Minors receiving a live adult donor kidney were excluded (n=37), resulting in 914 RT, including 30 patients receiving a second kidney and one patient receiving a third kidney.

In all our donors, renal vascular imaging was performed as part of standard preoperative screening. In most cases, imaging was performed in our center, however in 16.0% (n=152) cases, preoperative imaging was performed in a referring center. The current golden standard for imaging in most centers is CTA-angiography. However, before 2010, MRA was generally used to assess the anatomy of the donor. In some cases, both CTA and MRA were performed (i.e., due to claustrophobia, or failed imaging). DSA as a screening technique has been abandoned, however in our cohort it has been performed in a small number of cases for several reasons that could not be deduced.

Sensitivity, specificity, accuracy, positive- and negative predictive values were calculated for MRA and CTA. To discover any discrepancies in vascular anatomy between imaging and surgery, radiological and surgical reports were compared regarding vascular anatomy.

Results of the preoperative imaging and intraoperative findings during live donor nephrectomy were correlated to several intraoperative and postoperative (surgical) outcome measures (warm ischemia time (WIT), estimated blood loss, skin-to-skin time, complications, alteration of operative technique, re-operations, length of stay, re-admission, rise in serum creatinine). Donor complications were classified according to the Clavien-Dindo classification.[26]

Furthermore, intraoperative findings regarding anatomy during donor nephrectomy were correlated to several intraoperative and postoperative outcome measures of RT recipients (WIT, estimated blood loss (EBL) in milliliters, skin-to-skin time, complications (scored by Clavien-Dindo), length of stay (from postoperative day one to day of discharge), 30 day re-admission rate, creatinine drop (in µmol/l, comparing preoperative values with values of the first day after surgery and with one year postoperatively), primary non-function (PNF, defined as permanent absence of graft function), delayed graft function (DGF, defined as the need for dialysis within seven days after transplantation), BPAR (defined

as biopsy-proven acute rejection within three months after transplantation), diuresis of the graft on the operation table, and several other (urological) complications amongst which postoperative wound infection, wound dehiscence, urinary tract infection, urosepsis and obstruction/removal of the percutaneous nephrostomy). Since serum creatinine values can vary drastically depending on the time since last dialysis, we have chosen to include only preemptive recipients in the analysis of serum creatinine.

Several surgical techniques for donor nephrectomy are practiced in our center: transperitoneal laparoscopic donor nephrectomy with and without hand-assistance, hand-assisted retroperitoneoscopic donor nephrectomy and robot-assisted transperitoneal laparoscopic donor nephrectomy using the Da Vinci Surgical System. The exact procedures are described in the supplemental data. No (mini-)open donor nephrectomies have been performed since 2005.

Statistical analysis

All analyses were conducted using IBM SPSS Statistics for Windows, Version 21.0. (IBM Corp. Released 2012. Armonk, NY: IBM Corp.) Categorical variables were compared using the Chi-square test and continuous variables were compared with the Mann-Whitney *U* test or the independent samples t-test. Graft- and patient survival were expressed using Kaplan-Meier curves, and were compared using the log-rank test. *P*-values less than 0.05 were considered statistically significant.

The definitions of sensitivity, specificity, negative- and positive predictive value and accuracy are as follows; Sensitivity: probability that the scan is positive for vascular multiplicity and that there is actually vascular multiplicity found during the operation. Specificity: probability that the scan is negative for vascular multiplicity when there is indeed no vascular multiplicity during donor nephrectomy. Positive predictive value: probability that vascular multiplicity is present when the scan is positive. Negative predictive value: probability that vascular multiplicity is not present when the scan is negative. Accuracy is calculated from the combination of the sensitivity and specificity.

RESULTS

Regarding the donor baseline characteristics, of the 951 donors, 713 (75%) had single vascular anatomy of the kidney that was selected for donation. Of the other twenty-five percent, 139 (58.4%) had bilateral vascular multiplicity. Left-sided vascular multiplicity was present in 139 (23.5%) of the left kidneys, while right-sided vascular multiplicity was present in 99 (27.6%) of the right kidneys. 44.5% was male and the mean age of the donors was 52 years. In 592 (62.3%) of the donors, the left kidney was chosen. No significant differences in age, sex, Body Mass Index (BMI), choice of kidney side, ASA-classification (American Society of Anesthesiologists-classification), or surgical technique were observed between donors with single anatomy versus vascular multiplicity (Table 1). Regarding RT recipients baseline characteristics, of the 914 recipients, 64.6% was male and the mean age of the recipients was 51.3 years. No differences were found in gender, age, body mass index (BMI, relation with the donor, preoperative serum creatinine or the percentage of preemptive transplantations (Table 2).

TABLE 1. Baseline characteristics of living kidney donors.

	All live donors (n=951)	Donors with single vascular anatomy (n=713)	Donors with vascular multiplicity (n=238)	*P*-value
Gender (male; female)	423 (44.5%) 528 (55.5%)	306 (42.9%) 407 (57.1%)	117 (49.2%) 121 (50.8%)	0.093
Age (years)	52 (± 13)	52 (± 13)	51.4 (± 12.9)	0.543
ASA classification (I;II;III)	544 (61.7%) 333 (37.8%) 5 (0.6%)	410 (61.6%) 253 (38.0%) 3 (0.5%)	134 (62.0%) 80 (37.0%) 2 (0.9%)	0.706
Body Mass Index (kg/m^2)	26.2 (± 3.8)	26.2 (± 3.8)	26.2 (± 3.9)	0.982
Preoperative serum creatinine (µmol/L)	74.36 (± 13.7)	74.24 (± 13.8)	74.92 (± 13.6)	0.510
Kidney (left; right)	592 (62.3%) 359 (37.7%)	45 (63,5%) 260 (36.5%)	139 (58.4%) 99 (41.6%)	0.157

TABLE 2. Baseline characteristics of KT recipients.

Recipient characteristics	All recipients (n=914)	Recipients receiving kidney with single vascular anatomy (n=688)	Recipients receiving kidney with multiple vascular anatomy (n=226)	*P*-value
Gender (male; female)	589 (64.4%) 325 (35.6%)	449 (65.3%) 239 (34.7%)	140 (61.9%) 86 (38.1%)	0.366
Age	50.9 (14.4)	51.8 (14.1)	50.2 (15.3)	0.138
BMI	25.9 (4.7)	26.1 (4.6)	25.5 (4.9)	0.109
Relation (specified direct; specified indirect; unspecified)	711 (77.8%) 136 (14.9%) 67 (7.3%)	532 (77.3%) 108 (15.7%) 48 (7.0%)	179 (79.2%) 28 (12.4%) 19 (8.4%)	0.406
Preoperative serum creatinine	643 (312)	641 (316)	652 (299)	0.654
Preemptive transplantation	366 (40.0%)	278 (40.4%)	88 (38.9%)	0.554

Preoperative imaging compared with intraoperative findings

Preoperative imaging was divided as follows: MRA: 52.5% (n=499), CTA: 45.5% (n=433), DSA: 1.1% (n=10) and both MRA and CTA: 0.9% (n=9). A graphical overview of the preoperative scanning modalities over the years is provided in the supplemental data (supplemental figure 5). In 84.0% (n=799), preoperative imaging was performed in our center (MRA 56.7% (n=453), CTA 41.3% (n=330), DSA 1.1% (n=9) and both MRA and CTA 0.9% (n=7)). In 16% (n=152) donors, preoperative imaging was performed in a referring center (MRA 30.3% (n=46), CTA 67.8% (n=103), DSA 0.7% (n=1) and both MRA and CTA 1.3% (n=2)). Most donors (75%) had single anatomy (one artery, one vein). The division of other anatomical combinations of renal arteries and veins as determined intraoperatively is provided in Figure 1. In 139 donors (58.4%), vascular multiplicity was present bilaterally.

Regarding the assessment of the arterial anatomy, sensitivity and specificity for MRA were 65.6% and 98.3%. Sensitivity and specificity for CTA were 84% and 98%. Regarding venous imaging, sensitivity and specificity for MRA were 65.2% and 98%. Sensitivity and specificity for CTA were 79.5% and 98.7%. An overview of the accuracy of both modalities regarding arterial and venous anatomy is provided in Table 3A. No differences were found between scans performed in the Erasmus MC and scans performed elsewhere (Table 3B).

The left kidney was selected for donation in 62.3% (n=592) of the donors. An overview of the chosen kidney side over the years is provided in the supplemental data. In our center, over the years, the left kidney is chosen more often.

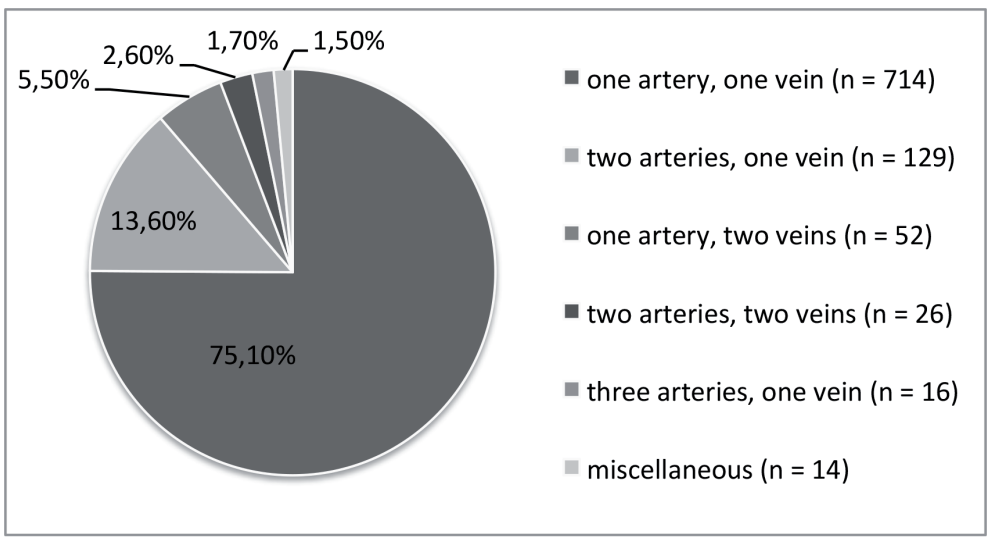

FIGURE 1. Variation in renal vascular anatomy as determined during live donor nephrectomy.

Clinical consequences of vascular multiplicity for the donor

Donors with AM had a significantly longer WIT (5.1 minutes versus 4.0 minutes, *P*=0.016) and skin-to-skin-time (202 vs. 178 minutes, *P*<0.001) compared with donors with a single renal artery (SRA). No significant differences were found in EBL, complication rate, conversion to an open operative technique, reoperations, length of postoperative hospital stay, and readmission. VM had no significant impact on WIT, EBL, conversion to an open operative technique, reoperations, length of postoperative hospital stay, or readmissions. VM did have a significant impact on skin-to-skin time (203 minutes vs. 180 minutes, *P*<0.001) and complication rate (17.2% vs. 8.4%, *P*=0.027) (Table 4). The significance of complication rate in VM disappeared when Clavien-Dindo grade I complications (predominantly infections of the Pfannenstiel incision, hematoma formation at the incision site (opened at the bedside), and urinary

TABLE 3A. Imaging results compared with intraoperative findings.

	MRA (arteries)	CTA (arteries)	MRA (veins)	CTA (veins)
Sensitivity	65.6%	84.0%	65.2%	79.5%
Specificity	98.3%	98.0%	98.0%	98.7%
Positive predictive value	89.7%	90.7%	76.9%	87.5%
Negative predictive value	92.6%	96.3%	96.5%	97.7%
Accuracy	**MRA (arteries)**	**CTA (arteries)**	**MRA (veins)**	**CTA (veins)**
Total	92.2%	95.3%	95.8%	96.7%
One artery/vein	98.3%	98.3%	98.0%	98.7%
Two or more arteries/veins	65.6%	82.9%	65.2%	79.5%

TABLE 3B. Accuracy of imaging comparing scans performed in our center to scans performed in referring centers.

Accuracy	Scan performed in Erasmus MC, arteries	Scan performed elsewhere, arteries	Scan performed in Erasmus MC, veins	Scan performed elsewhere, veins
Total	93.6%	92.8%	95.9%	95.4%
One artery/vein	98.0%	99.2%	98.3%	98.5%
Two or more arteries/veins	74.7%	67.7%	72.4%	66.7%

retention not requiring insertion of a urinary catheter) were removed. Thus, considering complications ranked grade II and higher, no significant differences are found (*P*=0.617).

In 32 (3.4%) cases, there was an intraoperative change in surgical technique. In 25 (2.7%) cases, single anatomy was present, and in 7 (0.6%) cases, the donor had vascular multiplicity. No significant differences were found. (*P*=0.614). In 10 (1%) cases, surgery was converted to open surgery, and in the remaining cases, conversion was done from laparoscopic transperitoneal to hand-assisted transperitoneal, HARP to laparoscopic, robot-assisted to HARP or laparoscopic and robot-assisted continued with a handport. No significant differences were observed between single anatomy and vascular multiplicity (*P*=0.186 for conversion to open technique, *P*=0.614 for alteration in surgical technique). When scored according to the Clavien-Dindo classification, overall complications occurred as shown in Table 5. One donor with a history of myocardial infarction who developed ventricular bradycardia immediately postoperatively, had to be resuscitated but unfortunately did not survive.

Clinical consequences of vascular multiplicity for the RT recipient

No significant differences were found in patient survival (*P*=0.148 for AM-donors and *P*=0.101 for VM-donors) and graft survival (*P*=0.610 for AM-donors and *P*=0.573 for VM-donors) (supplemental figures 1-4, median follow-up of 50 months). Patients receiving a kidney with AM had a significantly longer second WIT (25 minutes vs. 23 minutes, *P*=0.008) and total warm ischemia time (30 vs. 27 minutes, *P*=0.002). No significant differences were noted in skin-to-skin time, EBL, postoperative length of stay

TABLE 4. Intra- and postoperative outcome for donors with single renal arterial and venous anatomy compared with donors with multiple renal arteries and veins.

	Donors with single renal arterial anatomy (n=771)	**Donors with multiple renal arteries (n=180)**	***P*-value**
Warm ischemia time (minutes)	4.0 (2.2)	5.1 (5.7)	**0.016**
Estimated blood loss (ml)	151 (226)	207 (416)	0.099
Skin-to-skin time (minutes)	178 (48)	202 (45)	**<0.001**
Complication rate (Total number of complications according to the Clavien-Dindo classification)	68 (8.8%)	20 (10.1%)	0.339
Conversion to open technique	7 (0.9%)	3 (1.7%)	0.482
Reoperation	6 (0.8%)	2 (1.1%)	0.660
Postoperative length of stay (days)	3.44 (1.42)	3.50 (1.54)	0.639
Readmission	12 (1.6%)	4 (2.2%)	0.532
Difference in serum creatinine[a] (µmol/l)	41.4 (12.8)	40.6 (13.0)	0.457
Difference in serum creatinine[a] (%)	56.3% (16.3)	55.2% (17.3)	0.424
Difference in serum creatinine[b] (µmol/l)	34.6 (12.2)	35.7 (13.4)	0.334
Difference in serum creatinine[b] (%)	47.3% (15.7)	49.5% (18.5)	0.172
	Donors with single renal venous anatomy (n=862)	**Donors with multiple renal veins (n=89)**	***P*-value**
Warm ischemia time (minutes)	4.2 (3.3)	4.6 (2.8)	0.240
Estimated blood loss (ml)	161 (271)	168 (296)	0.802
Skin-to-skin time (minutes)	180 (47)	203 (50)	**<0.001**
Complication rate (Total number of complications according to the Clavien-Dindo classification)	72 (8.4%)	16 (17.2%)	**0.027**
Conversion to open technique	8 (0.9%)	2 (2.2%)	0.312
Reoperation	7 (0.8%)	1 (1.1%)	0.795
Postoperative length of stay (days)	3.44 (1.42)	3.60 (1.60)	0.289
Readmission	14 (1.6%)	2 (2.2%)	0.712
Difference in serum creatinine[a] (µmol/l)	41.3 (12,8)	40.1 (13.3)	0.405
Difference in serum creatinine[a] (%)	56.4% (16.5)	53.4% (15.9)	0.105
Difference in serum creatinine[b] (µmol/l)	34.8 (12.5)	34.4 (11.8)	0.798
Difference in serum creatinine[b] (%)	47.9% (16.3)	46.1% (15.3)	0.395

Continuous data represented as mean (sd).
[a]: Difference of serum creatinine between the first day after surgery and preoperative values.
[b]: Difference of serum creatinine between year one postoperative and preoperative values.

or 30-day readmission rate. Regarding venous anatomy, no significant differences were found in above-mentioned parameters when comparing single and multiple anatomy (Table 6).

No significant differences were found in occurrence of PNF, diuresis of the transplanted kidney on the operation table before wound closure, thrombosis rate or urologic complications (defined as: necessitating a percutaneous nephrostomy) when comparing single arterial anatomy and AM. The rate of

TABLE 5. Donor complication rate according to the Clavien-Dindo classification.

Grade	Percentage (n)	Percentage in donors with single anatomy (n)	Percentage in donors with multiple anatomy (n)
No complications	90.7% (863)	91.7% (654)	87.8% (209)
Grade I	4.5% (43)	3.9% (28)	6.3% (15)
Grade II	3.5% (33)	3.2% (23)	4.2% (10)
Grade IIIa	0.1% (1)	0.1% (1)	0%
Grade IIIb	0.8% (8)	0.7% (5)	1.3% (3)
Grade IVa	0.2% (2)	0.3% (2)	0%
Grade IVb	0%	0%	0%
Grade V	0.1% (1)	0%	1 (0.4%)

DGF was significantly increased in non-preemptive renal transplant recipients receiving a kidney with AM (*P*=0.018). Interestingly, recipients of a kidney with single arterial anatomy had a significantly higher rate of BPAR (*P*=0.012). This is an interesting finding that we cannot explain as the mean number of

TABLE 6. Intra- and postoperative outcome of patients receiving kidneys with either single or multiple arterial or venous anatomy.

	Single arterial anatomy (n=740)	**Multiple arterial anatomy (n=174)**	***P*-value**
2nd WIT (minutes)	22.75 (8.02)	24.98 (10.10)	**0.008**
Total warm ischemia time (minutes)	26.73 (8.51)	30.02 (12.91)	**0.002**
Estimated blood loss (ml)	403.02 (489.72)	453.26 (706.00)	0.396
Skin to skin time (minutes)	132 (36)	135 (32)	0.515
Creatinine drop (µmol/l)[a]	291 (45%)	279 (40%)	0.666
Creatinine drop (µmol/l)[b]	489 (74%)	515 (74%)	0.606
Postoperative length of stay (days)	14.47 (10.87)	14.49 (9.28)	0.983
Readmission within 30 days	134 (19.5%)	39 (17.3%)	0.454
	Single venous anatomy (n=833)	**Multiple venous anatomy (n=81)**	***P*-value**
2nd WIT (minutes)	23.08 (8.57)	24.15 (7.72)	0.283
Total warm ischemia time (minutes)	27.22 (9.75)	28.93 (8.14)	0.133
Estimated blood loss (ml)	416.52 (551.08)	372.60 (374.58)	0.506
Skin-to-skin time (minutes)	133 (35)	136 (39)	0.562
Creatinine drop (µmol/l)[a]	290 (45%)	261 (41%)	0.466
Creatinine drop (µmol/l)[b]	493 (74%)	483 (75%)	0.155
Postoperative length of stay (days)	14.52 (10.87)	14.04 (7.10)	0.698
Readmission within 30 days	59 (8.6%)	22 (9.7%)	0.599

[a]: Difference of serum creatinine in preemptive RT recipients between the first day after surgery and preoperative values

[b]: Difference of serum creatinine in preemptive RT recipients between year one postoperative and preoperative values

HLA-mismatches was exactly the same in the whole group (a mean of 3.3 HLA-mismatches, *P*=0.885) and no significant differences were seen between mean HLA-mismatches in the BPAR-group comparing AM with a single artery (*P*=0.511, data not shown). Moreover, the percentage of retransplantations in recipients suffering from BPAR in the single arterial anatomy group was not significantly higher (*P*=0.945, data not shown). No significant differences were found in occurrence of diuresis before wound closure, thrombosis rate, PNF rate, PCN-insertion rate, or rejection rate when comparing single venous anatomy

TABLE 7. Postoperative outcome of kidney transplant patients comparing single and multiple arterial or venous anatomy.

	Single arterial anatomy (n=740)	**Multiple arterial anatomy (n=174)**	***P*-value**
Diuresis directly after reperfusion (yes; minimal)	643 (91.7%) 10 (1.4%)	48 (6.8%) 1 (0.6%)	0.640
Thrombosis	9 (1.2%)	4 (2.3%)	0.281
PCN	110 (15.0%)	22 (12.7%)	0.446
PNF	4 (0.5%)	2 (1.1%)	0.371
DGF[1]	30 (6.9%) (n=437)	15 (13.9%) (n=108)	**0.018**
BPAR	103 (13.9%)	12 (6.9%)	**0.012**
Mean number of HLA-mismatches	3.3	3.3	0.885
Retransplantations	25 (3.4%)	6 (3.4%)	0.963
Wound infection	18 (2.4%)	5 (2.9%)	0.749
Wound dehiscence	7 (0.9%)	0 (0.0%)	0.196
Splint obstruction/removal	27 (3.6%)	12 (6.7%)	0.063
Urinary tract infection	125 (16.9%)	31 (17.7%)	0.800
Urosepsis	13 (1.8%)	2 (1.1%)	0.564
	Single venous anatomy (n = 833)	**Multiple venous anatomy (n=81)**	***P*-value**
Diuresis directly after reperfusion (yes; minimal)	729 (91.9%) 10 (1.3%)	68 (89.5%) 1 (1.3%)	0.735
Thrombosis	11 (1.3%)	2 (2.5%)	0.401
PCN	121 (14.6%)	11 (13.8%)	0.831
PNF	6 (0.7%)	0 (0.0%)	0.443
DGF[1]	39 (7.9%) (n=494)	6 (11.8%) (n=51)	0.339
BPAR	105 (12.6%)	10 (12.3%)	0.946
Mean number of HLA-mismatches	3.3	3.1	0.07
Retransplantations	26 (3.1%)	5 (6.2%)	0.147
Wound infection	22 (2.6%)	1 (1.2%)	0.424
Wound dehiscence	6 (0.7%)	1 (1.2%)	0.630
Splint obstruction/removal	38 (4.5%)	1 (1.1%)	0.122
Urinary tract infection	141 (17.0%)	15 (18.1%)	0.799
Urosepsis	15 (1.8%)	0 (0.0%)	0.217

1. Analysis of DGF excluding preemptive transplantations. 2. Biopsy-proven acute rejection within 3 months after transplantation.

and VM. Regarding complication rate in the recipients, we examined: postoperative wound infection, wound dehiscence, urinary tract infection, urosepsis and splint obstruction/removal. No significant differences were found in incidence of these complications when comparing single and multiple arterial and venous anatomy (Table 7). If an accessory lower pole artery was present, it did not lead to an increased number of inserted percutaneous nephrostomies (P=0.409)

DISCUSSION

This study provides a meticulous overview and analysis of data of a large cohort of live kidney donors over a period of 8 years. In this time-period, only laparoscopic donor nephrectomies or other endoscopic techniques were performed, diminishing possible confounding. The findings of this study prove that renal vascular multiplicity in a living kidney donor should not be considered as a contraindication for kidney donation, provided an adequate preoperative workup has been performed, and the surgical team is experienced. From a radiological perspective, a CTA is the preferred imaging method, because of the predictive value of vascular multiplicity. WIT and skin-to-skin time are both significantly longer in donors with AM, and VM was only associated with a significantly longer skin-to-skin-time. In the VM group, the WIT was not longer, what can be explained by the fact that sometimes smaller accessory veins are ligated before ligating the renal artery, after which the WIT starts. However, the impact of AM/VM on clinical outcome is small to non-existent. Furthermore, we have found no significant difference in parameters that would impact a donors' outcome, such as alteration of operative technique, conversion to open technique, length of stay, likelihood of reoperation or need for readmittance. Although the complication rate was significantly higher for VM, this was only the case for Clavien-Dindo grade I complications. It has been postulated that the presence of lower pole arteries leads to more urological complications because of the fact that they normally vascularize the ureter. In contrast to the findings of Kok *et al.*, reporting a significantly increased risk of ureteral complications in patients with an accessory lower pole artery, in our cohort the presence of additional lower pole arteries did not lead to an increased number of inserted percutaneous nephrostomies.

In addition, CTA is clearly superior to MRA, both in sensitivity and accuracy, both regarding venous anatomy and arterial anatomy, concluding that CTA should be considered as gold standard regarding preoperative imaging. Looking at parameters related to recipient outcome, we found that AM/VM does not lead to increased morbidity and mortality. We also found no significant differences in intraoperative parameters such as EBL, or skin-to-skin-time in RT. Second WIT was significantly longer for kidneys with multiple renal arteries, however, not leading to impaired outcome for the recipient.

Recently, Omoto *et al*. have analyzed their cohort of 533 live kidney donors,[27] looking only at the number of renal arteries, showing that AM might increase slow graft function (defined as: serum creatinine level is more than 3.0 mg/dl at 4 days after transplantation) but not acute rejection rates. In our cohort, we have also analyzed the presence of multiple veins. In general, the incidence of slow (SGF) and delayed graft function is low in grafts procured from live kidney donors. The total rate of DGF in

our cohort was 5.1% (n=47). The incidence of DGF was significantly increased when transplanting a kidney with vascular multiplicity. One can argue whether these outcome measures are clinically relevant to analyze in grafts from live kidney donors, even if vascular multiplicity is present, because of the low incidence of DGF in kidneys from living donors. Furthermore, in our center, a large percentage (40.7%) of the donations is intended for preemptive transplantation In our cohort, the mean WIT is increased by only two minutes due to VM. More importantly, graft- and patient survival are not negatively influenced by vascular multiplicity.

Limitations

First, this study has a retrospective study design with all the limitations inherent to the lack of prospective follow-up, and we recognize the possibility of information bias.

Second, renal vascular anatomy may be misclassified since radiologists and transplant surgeons each might have a different way of judging anatomy. For example, a transplant surgeon might have a more functional look at the present anatomy. Early branching of a singular renal artery, thus requiring separate dissection and clamping of both arterial branches, might be classified as two renal arteries. This example might have been correctly seen by the radiologist as a single renal artery with early branching and noted as such. This example may lead to an incorrect false negative imaging result. To correct for this possibility, all false negative imaging results have been examined independently (JAL/MB). In case of doubt, cases were reviewed by a supervising author (FJMFD). The reverse is also possible, however. Early branching may be misdiagnosed by a radiologist as dual arteries.[28]

Third, considering the low number of donors presenting with rare anatomical variations (i.e. more than 3 arteries or veins, 3.1% total), no reliable conclusion can be made regarding the feasibility and safety of kidney donation in these cases. In our cohort, only 22 kidneys (2.3%) had three renal arteries and only one kidney (0.1%) had four arteries. Similarly, five kidneys (0.5%) had three veins, three (0.3%) had four veins and only one had five veins (0.1%) (Figure 1). Moreover, these donors were carefully selected, and we did not analyze the potential donors with vascular multiplicity that were excluded early in the screening process. Even in a high volume center as ours, with almost 1000 live donor nephrectomies performed in eight years, even higher numbers would be needed to get a sufficient insight in these rare anatomical variations. It would therefore seem prudent to create an international database containing information about these cases. Only in this way, we can collect enough information on the practice of live kidney donation to reliably assess potential donors presenting with these anatomical variations.

Last, we were not able to analyze the number of vascular reconstructions 'on the bench', because of the relatively scarce reporting of these interventions in the operation reports. In addition, the exact type of reconstruction made (e.g. side-to-side or end-to-side anastomosis, becoming increasingly complex with an increasing number of arteries or veins) was often unclear. One could imagine that the need for a reconstruction could possible lead to a higher incidence of complications in a recipient.

As stated in the introduction, only one guideline incorporated vascular multiplicity of possible live kidney donors (the British Transplantation Society).[15] Although several studies have looked into vascular

multiplicity, still, no hard statements are written regarding this issue. Some studies show an increased incidence of (ureteral) complications in recipients,[9,29] whilst other show good outcome.[10,27,30-32]

By performing this analysis of our cohort of a high number of live kidney donors and recipients, in conclusion, we have shown that CTA is superior to MRA in regards to preoperative kidney donor screening. Live donor nephrectomy is a safe procedure for the donor, even with vascular multiplicity. Although vascular multiplicity is in most centers considered as a relative contraindication to donation, based on our results we conclude that it should not be considered a contraindication at all. Obviously, robust screening is warranted in potential live kidney donors to ensure donor safety. Furthermore, in contrast to published literature,[5,11,25] RT recipients receiving a kidney from a live donor with vascular multiplicity have excellent outcome as well, and no increased risk for urological complications.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose.

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Chapter 9

Donors with stone-bearing kidneys are eligible for living kidney donation: A systematic review and cohort analysis

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ABSTRACT

Background Since living kidney donation can still not meet the demand for donor organs, extended criteria donors are increasingly included, such as donors with one or more kidney stones. Little is known about the outcome of these donors, as a possible future risk exists that recurrent stones, obstructions, and infections could injure the remaining kidney. Furthermore, the outcome of renal transplant recipients that retrieve a kidney with stones is of great importance as inadvertent transplantation could also impair recipient outcome.

Methods Comprehensive searches were carried out in several databases up to December 2014 to search for relevant articles. We evaluated current guidelines for donors with stone disease and data to review to which extend stone-bearing kidneys are eligible for living kidney donation. Furthermore, the cohort of 1,555 donor nephrectomies and transplantations in the center of the authors was analysed for outcome of donors and their recipients.

Results Of the 3,115 articles found, 18 met the inclusion criteria. Based on the literature search, both in attitude and in practice there is a shift in accepting more donors with (a history of) kidney stones. The prevalence in the literature ranges from 0.6% to 7%. In our cohort, the prevalence of kidney stones was 2.3% (36 live kidney donors). 21 donations of stone-bearing kidneys took place, of which 3 donors developed a stone-related event, which all passed without intervention. Three of the recipients developed a stone-related complication, which were all successfully treated.

Conclusion We conclude that asymptomatic stone-bearing kidneys seem to be suitable for donation and transplantation. Both donors and recipients have excellent outcome. However, a sufficient follow-up is required to confirm these outcomes in the long-term. We would advise that current guidelines are revised to remove stone-bearing kidneys as an absolute contraindication for donation and transplantation.

INTRODUCTION

The incidence and prevalence of end-stage renal disease (ESRD) is a worldwide increasing problem.[1,2] This is due to an increase in the prevalence of risk factors like diabetes, hypertension and obesity.[1-3] Kidney transplantation remains the golden standard as treatment for patients with ESRD. It provides a better quality of life and higher survival rates compared with dialysis.[4,5] In addition, the number of deceased kidney donors alone is not enough to cope with the increasing donor organ shortage.[6] Over the past decades, transplant professionals have performed many evaluations of (potential) donors, by which they have gained a lot of individual experience regarding this topic. However, there is little consensus and no communal accepted protocols with respect to preoperative screening of donors among transplant centers.[7] This aspect is very important, because living kidney donation has already proven to successfully increase the donor pool. Therefore, careful selection of live kidney donors remains warranted. Since there are many ESRD patients that remain on the waiting list for kidney transplantation, there is a shift in accepting more donors with comorbidities, so-called extended criteria donors.[8] Some examples are overweight/obese donors,[9-13] hypertensive donors,[10,14-17] donors with older age,[13,18-21] or donors with vascular anomalies/multiplicity.[22-25] Also, the procedure of living kidney donation creates an ethical dilemma because of its unique situation in which the individual undergoing this procedure has the potential for harm with no physical benefit.[26]

Another phenomenon that can be qualified as an extended criterion is the presence of one or more kidney stones in a donor (nephrolithiasis). Compared with traditional renal donor radiographic modalities (e.g., intravenous pyelography (IVP) and angiography), CT angiography (CTA) scans are more sensitive and specific for detecting renal abnormalities, resulting in more findings of kidney stones in the preoperative screening process.[27-30] Nowadays, CTA has become a clinical accepted modality for preoperative evaluation of potential kidney donors.[28,29,31-34] With regard to this, some transplantation centers consider CTA as the gold standard.[35] Annual incidence rates of kidney stones in the general population are approximately three cases per 1,000 individuals in men, and one to two cases per 1,000 individuals in women.[36] The lifetime risk for kidney stone disease currently exceeds 6–12% in the general population.[36] The global prevalence appears to increase steadily in both sexes and the last numbers ranges between 1.7% and 14.8%.[37] One of the possible complications of kidney stones is an infection or obstruction which may lead to kidney damage.[38] Importantly, in the absence of medical treatment, kidney stone formation is a recurrent disease in 20% and 31% of these patients in 5 and 10 years, respectively.[39] To underline this problem, it is known that for about 10% of patients with kidney stones have to deal with more than three episodes of recurrence.[40] More specifically, with regard to patients with asymptomatic kidney stones, 77% had experienced progression to symptomatic kidney stone disease with 26% requiring surgical intervention (e.g., percutaneous nephrolithotomy, ureteroscopy, or shockwave lithotripsy).[41] Beside these findings, several studies determined the clinical characteristics in patients with symptomatic kidney stones. Symptomatic stones have been associated with many systemic conditions like hypertension,[42,43] hyperparathyroidism,[44] metabolic syndrome,[45-47] diabetes mellitus,[48] obesity,[49,50] gastric

bypass,[51] and chronic kidney disease.[52-54] These patients are also characterized by older age, male gender and Caucasian race.[36,55]

There are several guidelines available that address selection criteria for live kidney donors.[56-60] These guidelines generally state that an asymptomatic potential donor with a current (or a history of) single stone may be suitable for donation.[56,57,60] However, such potential kidney donors should be screened for metabolic stone forming abnormalities (e.g., hypercalcuria, hyperuricemia, hyperoxaluria, hyperuricosuria, hypocitraturia, cystinuria, and metabolic acidosis).[57,60] Furthermore, guidelines state that potential donors with (a history of) bilateral stone disease or an infection-related (struvite) or cysteine kidney stone generally should not be considered suitable for kidney donation.[57,58,60] Moreover, it is important to discuss the risks and benefits of donation with both the potential donor with asymptomatic stones and the recipient.[61] However, common recommendations concerning acceptance of live kidney donors with stones are sparse. Furthermore, practice and attitudes differ between transplant centers (Lafranca *et al.,* submitted).[62-64]

If there is a monolateral kidney stone present in a potential donor, it feels naturally to choose this kidney for donor nephrectomy, as we want to maintain the best kidney for the donor. However, it is not known whether stone formers who donate a kidney have worse outcome with respect to renal function compared with stone formers with two kidneys. The possible options in treating kidney stones before and after transplantation consist of shock wave lithotripsy or percutaneous nephrolithotripsy.[65-67] However, the optimal management of stone-bearing kidneys during bench surgery before implantation (e.g. *ex vivo* ureteroscopy (ExURS)) is unclear and not agreed upon in the transplant community.[57] To elaborate aforementioned technique, in 2006, a consultant transplant urological surgeon was appointed to perform ExURS. Since then, this technique was performed where appropriate to remove kidney stone(s) on the bench before transplantation in some centers. However, what is the outcome for transplanted kidneys with stone(s) left in situ? Should we try to remove these stones ex vivo prior to transplantation?

In this systematic review and cohort analysis, we reviewed current guidelines for donors with stone disease as well as all relevant literature on stone related morbidity in donors with stone disease and recipients who received a kidney with a stone left in situ. We also examined the prevalence of asymptomatic stones in the cohort of live kidney donors of the Erasmus MC. We assessed the long-term outcome of these living (un)specified donors and their respective recipients in our center. Furthermore, we tried to retrieve some answers on the above described questions, to see if we can safely expand the donor pool by including live kidney donors with kidney stones, but in the process ensuring that a healthy donor does not become a patient.

METHODS

All aspects of the Cochrane Handbook for Interventional Systematic Reviews were followed.

Literature search strategy

Comprehensive searches were carried out in Medline OvidSP, Embase, CENTRAL (the Cochrane Library 2014, issue 12), Web-of Science, Google Scholar, and Pubmed Publisher. The search was performed for articles published up to December 2014 relevant to outcome of live kidney donors with kidney stones as well as the recipients of a transplanted kidney with stones. The search terms were specific to each search engine, which is supplied in the Supplementary Data. In addition, manual reference checks of included articles were performed to check for potentially missing studies. We were interested in the outcome of live donor nephrectomy and therefore excluded articles regarding deceased kidney donors with kidney stones. Furthermore, we included studies describing outcome of transplanted kidneys with one or more stones in renal transplant recipients.

Literature screening

Articles were screened and evaluated by three independent researchers (SFD, OI, JAL) for possible inclusion and relevance to the subject. A random check was performed by a senior investigator (FJMFD). All selected articles were screened for relevance, utility, and reliability. Inclusion of a study required: 1) articles describing kidney stones in (potential) live kidney donors, and 2) articles describing outcome in recipients. If any discrepancies in inclusion or exclusion occurred, a senior investigator (FJMFD) was consulted.

Data extraction and critical appraisal

The level of evidence of each paper was established following the Oxford Centre for Evidence-Based Medicine Level of Evidence scale and by using the GRADE tool. The GRADE approach defines the quality of a body of evidence by consideration of within study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias.

Cohort data collection and statistical analysis

A retrospective cohort analysis was performed on all live kidney donors who underwent donor nephrectomy between January 1994 and January 2015 at the Erasmus MC, Rotterdam, the Netherlands (n=1555). During this period, the preoperative imaging (mostly by MRA or CTA) was performed at either our center or a referring center. The radiographic findings were reported or re-reviewed by our radiologists. Live kidney donors with asymptomatic stones were identified through critically reviewing the preoperative imaging and their reports. For each of these live kidney donors and their prospective recipients, the patient characteristics and data were extracted from the electronic hospital system.

The follow-up period was measured from time to surgery to: 1) the time of most recent follow-up (e.g. most recently outpatient visit or telephone contact), 2) time to death, or 3) time to transplantectomy. Descriptive continuous variables were summarized using medians and ranges. Descriptive categorical

TABLE 1. Results of ten articles investigating the transplantation of stone-bearing kidneys and their donors.

Author	Year	Number of living (un)-related transplants (time period)	Number of stone forming donors proceeded with kidney donation	Number of transplantations of a stone-bearing kidney	Stone size range (mean)	Stone location	Follow up range (mean)	Complications in recipients	Complications in donors
Kumar[70]	2003	1011 (13.5 yrs.)	6	5	<1 cm	pelvis	0.3-7.4 yrs. (3.26 ± 0.6 yrs.)	None (all underwent postoperative lithotripsy)	1 (after 2 years: stone in lower ureter, anuria)
Devasia[71]	2005	N/A (2 yrs.)	5	4	3-4 mm (3.75 mm)	N/A	1-2 yrs.	None	N/A
Ho & Chow[72]	2005	710 (4 yrs.)	44	44 (13 were followed with CT scan)	1-6 mm	N/A	(21 months)	1 (1 mm stone growth to 8 mm; recurrent urinary tract infections)	N/A
Martin[73]	2007	N/A (2 yrs.)	5	5	< 4mm	3 upper pole, 2 mid-pole, 2 lower pole	(508±313 days for donor) (711±334 days for recipient)	None	None
Strang[74]	2008	118 (1 yrs.)	10	10 (9 were followed)	1-5 (2.1mm)	N/A	(11.2 months for donor) (9.8 months for recipient)	None	None
Srivastava[75]	2010	N/A (9 yrs.)	16	5	< 4 mm	N/A	1-3 yrs.	None	N/A
Patel[76]	2011	167 (6 yrs.)	10	5	2-8 mm (4 mm)	N/A	24 months median	None	None
Kim[77]	2012	294 (10 yrs.)	16	11	1-9mm (3 mm)	parenchymal regions of the upper /lower poles-interpolar regions	1-3 yrs. for donor 0.25-1 yr. for recipient	1 (obstructive symptomatic kidney stone disease)	None
Rizkala[78]	2013	732 (10 yrs.)	54	41	1-6 mm (2.4 mm)	9 upper pole, 13 mid-pole, 5 mid-lower pole, 11 lower pole	22.5 months median for donors 47.4 months median recipient	None	None
Olsburgh[79]	2013	N/A (7 yrs.)	20	3	1-12 mm (3.1 mm)	5 upper pole, 5 interpolar, 10 lower pole	12-49 months for donors (26 months) 1-24 months CT/US imaging for recipient (10 months) + US at 37 month	None	None

variables were summarized using frequencies and percentages. All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 21.0.0.1 (IBM Corp. Released 2012. Armonk, NY: IBM Corp.).

RESULTS

Literature search

The initial search identified 3,115 records. Of these, 1,321 were duplicates and 1,794 articles remained. After the first and second phase (title and abstracts review), 1,747 articles were ineligible for this review. In the third phase, the remaining 47 articles were retrieved and reviewed in full text with 18 articles found to be eligible and included in the final analysis. The PRISMA-flowchart is presented in Figure 1. The assessment of the quality of the available evidence using the GRADE tool is presented in Figure 2.

Trends and attitudes in kidney donation among kidney stone formers

The practice and attitudes differs between transplant centers.[62-64] With regard to this, Ennis *et al*. examined the current climate in the United States in the approach to dealing with stone formers who are evaluated for kidney donation.[68] To this survey, 77% (n=59) of the transplant centers allowed kidney donation of stone formers and 36.8% (n=28) had changed their attitude towards accepting donors with a history of or with current kidney stones over the last 5-10 years. Among these centers, 93% (n=26) were more likely to accept these donors. The same survey was repeated several years later and the rate of transplant centers that allowed donation from kidney stone formers increased from 74.7% to 80.8%. Thus, in both attitudes as in practice, there seems to be an increasing shift towards accepting more kidney donors with a history of or current kidney stones. In 2008, Giessing *et al.* performed a survey in all German kidney transplantation centers (n=28).[69] Ten of these centers regarded kidney stone disease at time of evaluation as an absolute contraindication for donation. Only one center maintained a history of kidney stone disease as a general exclusion criterion. Thereby, the length of the stone-free episode was relevant for 42% of the respondents (6 months-10 years). In addition, 50% of these respondents accepted a stone-free period less than two years and the other 50% accepted a stone-free period longer than two years. The potential living donors with a history of kidney stone disease were evaluated through specific tests including different imaging techniques (e.g. MRA, CTA, or IVP), metabolic work-up and urodynamic evaluation used by 82% of the centers.

Outcome of transplantation of stone-bearing kidneys and their donors

To date, few articles have been published regarding the outcome of transplanted kidneys with stone(s) left in situ. Table 1 provides an overview of the outcome of stone-bearing kidneys and their donors of these studies.

Kumar *et al.* retrospectively reviewed 1,011 living related kidney transplants.[70] Only five stone-bearing kidney donors donated without any intraoperative intervention for the stone. These five recipients

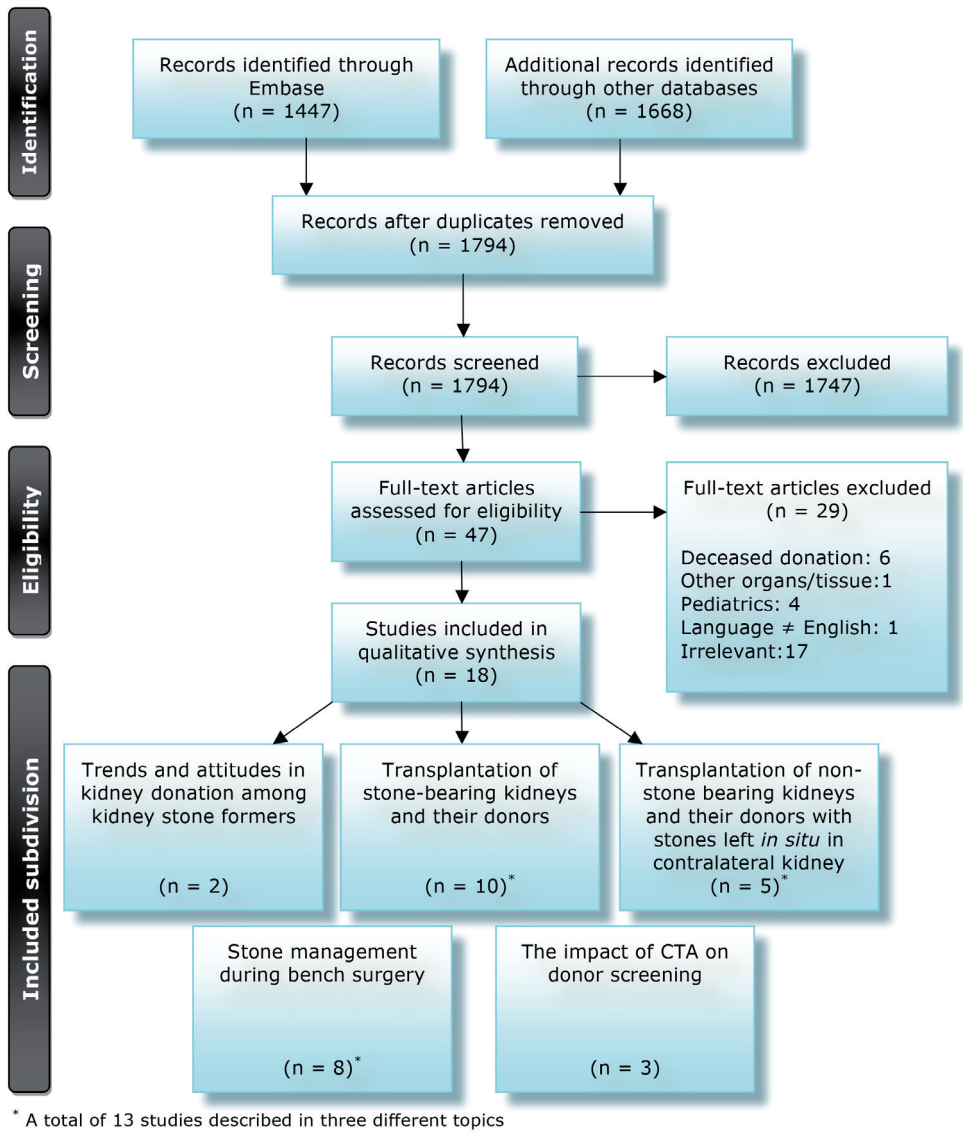

FIGURE 1. PRISMA-Flowchart.

underwent postoperative lithotripsy. Both donors and recipients had a mean follow-up of 3.26 ± 0.6 years. Only one donor developed a complication after two years: anuria caused by a stone in the ureter, which was ureteroscopically removed. None of the recipients reported a recurrence of stone disease or other adverse events. In 2005, Devasia *et al.* published the outcome of four stone-bearing live kidney donors with an asymptomatic solitary stone, who donated during a 2-year period.[71] These donors had

Kidney stones in live kidney donation						
Quality assessment						
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence
Trends and attitudes (measured with: Surveys; Better indicated by lower values)						
104 (2 studies[1]) 2 years[3]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊖⊖⊖ **VERY LOW**[2] due to risk of bias
Transplantation of stone-bearing kidneys (Better indicated by lower values)						
133 (10 studies[5]) 0-7.4 years	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊖⊖ **LOW**
Transplantation of non-stone bearing kidneys (Better indicated by lower values)						
16 (5 studies[5]) 0-3 years	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊖⊖⊖ **VERY LOW**[7] due to risk of bias
Stone management during bench surgery (Better indicated by lower values)						
59 (8 studies[5]) 0-7.4 years	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊖⊖ **LOW**
Impact of CTA on donor screening (Better indicated by lower values)						
2390 (3 studies) 7 years[10]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊖⊖ **LOW**

[1] Two survey studies.
[2] Subjective information in surveys.
[3] Two surveys, publication range 2008-2009.
[4] Seven retrospective cohort studies, two case-series, one prospective cohort study.
[5] A total of thirteen studies described in three different topics.
[6] Four retrospective cohort studies, one prospective cohort study.
[7] Small sample size.
[8] Four retrospective cohort studies, three case series, one prospective cohort study.
[9] Three retrospective cohort studies
[10] Three retrospective cohort studies, publication range 2007-2014

FIGURE 2. GRADE-tool assessment.

no history of stone disease. Prior to the transplantation of a kidney with a 12 mm stone, lithotripsy was performed six weeks before transplantation. This stone-bearing kidney was transplanted with a residual fragment of 4mm. However, three other donors had no intraoperative intervention. The recipients were followed up for maximum 2 years and none had an (stone-related) adverse event or recurrence of stone disease. In 2005, Ho and Chow reported 44 stone-bearing donors in a series of 710 donated kidneys during a 4-year period (6%).[72] Only 13 recipients were followed up postoperatively with a CT scan. Of these recipients, five showed no stones, four showed a stable stone size and four increased in size. None of the recipients developed graft loss or morbidity due to obstruction due to a kidney stone at a mean follow-up of 21 months. In 2007, Martin *et al.* evaluated the possible adverse events in five patients who underwent kidney transplantation with kidneys containing asymptomatic calculi from living donors.[73] None of these donors had a history of stone disease. There were a total of eight stones in five patients. Neither the donors nor the recipients reported a recurrence of stone disease or other (stone-related) adverse events at a mean follow-up of 508 ± 313 days and 711 ± 334 days, respectively. Nevertheless, the follow-up CTA showed spontaneous passage of the stones in three recipients (five stones). The other three stones were still *in situ* in two recipients**,** but they had a significantly shorter follow**-**up period

(204 ± 72 days vs. 711 ± 200 days, $P<0.05$). In 2008, Strang *et al.* published that ten live kidney donors with a solitary, asymptomatic calculus were accepted for donation.[74] None of the donors and recipients experienced a stone-related adverse event or recurrence of stone disease during a follow-up period of 11.2 and 9.2 months, respectively. In 2010, Srivastava *et al.* reported five patients with asymptomatic kidney stones donated with stones *in situ*.[75] During the follow up with CTA, two recipients had persistent residual stones at three months and one recipient within one year. In addition, none of the recipients experienced any stone-related complications. In 2011, Patel *et al.* reported a total of five donors who donated their stone-bearing kidney during a 6-year period.[76] In addition, none of the donors and recipients experienced any stone-related complications or other adverse events during a median follow-up of 24 months. In 2012, Kim *et al.* published a group of 294 potential kidney donors, screened with MRA or CTA, who proceeded to donation.[77] A total of eleven donors donated their kidney with stone(s) *in situ*. Only one of these recipients (with an allograft containing 9mm stone) developed symptomatic kidney stone disease three months after transplantation. Ultrasound showed two newly formed stones secondary to hyperoxaluria causing obstruction at the mid-ureter. This recipient underwent percutaneous nephrostomy tube placement. The donor of this allograft reported no symptoms of stone disease and a stable kidney function three year after donation. None of the remaining ten donors and recipients developed symptomatic kidney stone disease or other (stone-related) adverse events during a follow up of 1-3 years and 0.25-1 year, respectively. In 2013, Rizkala *et al.* performed a study to determine the outcomes of living-related donors with history or presence of kidney stone disease and their respective recipients.[78] A total of 54 donor-recipient pairs met the inclusion criteria during a period of 11 years. Seven donors and four recipients had previous symptomatic kidney stone disease. Of the 54 donors, 41 patients donated a kidney with at least one stone. They observed the donors and recipients with a median follow-up of 22.5 months (IQR 1-79.3) and 47.4 months (IQR 25.1-76.1). Furthermore, 50% of the donors and 77.7% of the recipients had a follow-up of more than two years. During the follow-up period, neither 41 donors who donated a kidney with at least one stone nor their recipients had any stone episodes or other (stone-related) adverse events. In another study performed by Olsburgh *et al.* (2013), there was a prevalence of 5% of kidney stones among 377 potential kidney donors.[79] In addition, an extra 36 potential donors with kidney stones were added from other centers. During a 7-year period, a total of twenty donors with kidney stones proceeded to donation. Among these donors, only three stone-bearing kidneys were transplanted with the stone *in situ*. The donors were followed-up by imaging (either ultrasonography or CTA) with a mean (range) follow-up of 26 (12-49) months. None of the donors had experienced a stone recurrence or stone-related complication and no stones were detected on imaging of eight donors with >1-year follow-up. The recipients of the three stone-bearing kidneys were also followed-up by imaging. One recipient had a stable stone on CTA at 49 months follow-up and in two recipients no stones were detected on imaging at 21 and 55 months follow-up.

Outcome of transplantation of non-stone bearing kidneys and their donors with stones left in situ in the contralateral kidney

The articles presented above focused on the transplantation of stone-bearing kidneys. Nevertheless, it may occur that these kidneys cannot be transplanted due to different causes (e.g., surgeon preference, complex anatomy). In such cases, most of these donors underwent contralateral non-stone bearing donor nephrectomy. Patel *et al.* (2011) reported that in two cases the non-stone bearing kidney was donated due to challenging vascular anatomy of the other kidney.[76] During a median follow up of 24 months, none of these donors had any stone-bearing complications. In 2011, Vasdev *et al.* published an incidence of asymptomatic kidney stones of 3.2%.[80] In two cases, both donors voluntary decided to donate their non-stone bearing kidney. However, one of these recipients formed a stone at 48-month follow-up, which was ureteroscopically extracted. In a further follow-up of 12 months following the intervention, this recipient reported no other episode of stone disease. The other recipient was followed up for 72 months and experienced no episode of stone disease. Unfortunately, there was no follow-up data available for the two stone-bearing donors. Kim *et al.* described five stone-bearing kidney donors who donated the other kidney without the stone.[77] None of these donors reported symptoms or evidence of stone disease during a median follow-up of 5.3 years (SD 1.75 years). Rizkala *et al.* included six donors with right kidney nephrolithiasis who underwent left donor nephrectomies.[78] During the follow-up period, only one of these donors with a single kidney stone (2mm) in the right mid-pole who donated the left kidney experienced a stone episode, which spontaneously passed with intravenous fluids after visiting the emergency room. Otherwise, no other donors or their recipients had any stone episodes or other (stone-related) adverse events. Olsburgh *et al.* also described one case who voluntary decided to donate the non-stone bearing kidney.[79] The donor had a 1mm right lower pole stone in his solitary right kidney. This donor reported no stone-related complication but moved overseas and was lost to follow-up. Table 2 summarizes the results of these studies published between 2011 and 2013.

Stone management during bench surgery

Stone management of live donor kidneys during bench surgery is considered as an option. Kumar *et al.* observed one case where the stone was removed by a small pyelotomy after graft harvest.[70] The recipient had neither recurrence of stone disease nor other adverse events. In 2004, Rashid *et al.* performed a study to evaluate the safety and efficacy of *ex vivo* ureteroscopy (ExURS) during transplantation among ten living (un)related donor kidneys with unilateral asymptomatic stones.[81] In all ten cases, this technique was successfully performed except in one case where no stone was visualized. The remaining nine cases had a total of ten stones, of which nine stones were successfully removed with holmium laser lithotripsy (n=6) or endoluminal basketing (n=3). They found no intraoperative or postoperative ureteral complications. In addition, they observed no adverse effects on allograft function. The donors and recipients were followed up by imaging (ultrasonography, CTA, plain radiographs) with a mean follow up of 36.4 months (18-60 months) and 33.2 months (18-60 months), respectively. In both group of patients, there was no stone recurrence. In 2011, Vasdev *et al.* described the treatment of three stone-

TABLE 2. Results of four articles investigating the transplantation of non-stone bearing kidneys and their donors with stones left in situ.

Author	Year	Number of living related trans-plants (time period)	Number of stone forming donors proceeded with kidney donation	Number of transplantations of a stone-bearing kidney left in situ	Stone size in the stone-bearing kidney	Follow-up range (mean)	Complications in recipients with non-stone bearing kidney	Complications in donors with stone-bearing kidney in situ
Patel[76]	2011	167 (6 yrs.)	10	2	N/A	24 months median	None	None
Vasdev[80]	2011	157 (5 yrs.)	5	2	N/A	60-72 months	1 (developed a 7x2 mm kidney stone requiring stone extraction)	N/A
Kim[77]	2012	294 (10 yrs.)	16	5	< 2 mm	5.3 ± 1.75 yrs. for donor 0,25-1 yr. for recipi-ent	None	None
Rizkala[78]	2013	732 (10 yrs.)	54	6	N/A	22.5 months median for donors 47.4 months median recipient	None	1 (a 2 mm stone passed tspontane-ously)
Olsburgh[79]	2013	N/A (7 yrs.)	20	1	1 mm	12-49 months for donors (26 moths) 1-24 months CT/ US imaging for recipient (10 months) + US at 37 month	None	None (lost to follow-up)

N/A, not available

bearing donor kidneys using ExURS with a basket method.[80] In one case, the stone was extracted prior to transplant (Bench technique) with a warm ischemia time of 5 minutes and in the remaining two cases when the donor kidney graft was revascularized into the recipient (On-table technique). They observed that there was no evidence of recurrence of stone disease in both the live kidney donors and recipients at a mean follow-up of 64 months (range 48-64 months). Also, no complications were seen in the graft and urological function. Patel *et al.* described that three stone-bearing donor kidneys underwent intraoperative intervention (1 in-vivo, 2 ex-vivo) prior to transplantation using flexible ureteroscopy.[76] No intraoperative complications were reported and none of these donors or their recipients experienced any stone-related complications or other adverse events during a median follow-up of 24 months. Schade *et al.* reported their experiences with ExURS for the treatment of 23 small asymptomatic stone-bearing donor kidneys.[82] Stone extraction was performed with laser litotripsy (n=6) and basket extraction (n=12) of stone-bearing donor kidneys. Treatment rendered 17 of 19 stone-bearing kidneys stone free. No intraoperative complications occurred and the study reported only one postoperative ureteral complication (complete occlusion of the ureteroneocystotomy in an ureter without a stent). The recipients had adequate graft function at 1 month and 1 year postoperative as seen in the follow-up. Postoperative imaging studies showed no stone recurrence and delayed ureteral strictures among the recipients, at a median follow-up of 63 ± 47.2 months. Olsburgh *et al.* described a total of 17 donors who proceeded to ExURS. Only in ten cases the stone(s) were successfully removed.[79] The stones were extracted as follows: four cases with holmium laser, five cases with basket and one case (12mm stone) with a combination of holmium laser and basket. There was no recurrence of stone disease in the recipient kidney on ultrasonography at 37-months follow-up. Thereby, 70% (n=7) of ExURS had a follow-up imaging of either ultrasonography or CTA at a mean (range) of 10 (1-24) months. There were no early or late allograft stone-related complications and no evidence of stones. Rizkala *et al.* also reported a case of one donor who underwent a bench 'ex vivo' ureteroscopy and stone basket extraction of one stone of 2mm.[78] Neither the donor nor the recipient experienced recurrence of stone disease during a median follow-up of 22.5 months and 47.4 months, respectively. On the other hand, Devasia *et al.* described nephrolithotomy after perfusion of a donor kidney with a 15mm stone.[71] The recipient experienced no adverse events or recurrence of stone disease. Table 3 summarizes the results of these studies published from 2003 until 2013.

The impact of CT angiography on donor screening

Nowadays, almost all transplant centers evaluate their potential donors with CTA. This radiographic modality is more sensitive and specific for detecting renal abnormalities, e.g. asymptomatic kidney stones. Strang *et al.* studied the difference in the exclusion rate for potential live kidney donors evaluated with IVP, renal scan and renal arteriography (group 1) compared with CTA and renal scan (group 2).[83] In group 1 and group 2.7% vs. 16% of the potential donors were excluded because of radiographic abnormalities (P<0.01). Regarding the potential donors with kidney stones, 1% (three unilateral and one bilateral) and 7% (12 unilateral and 10 bilateral) were excluded in group 1 and 2, respectively. In 2014, Beniwal *et*

TABLE 3. Results of eight articles investigating stone management during bench surgery.

Author	Year	Number of stone forming donors proceeded with kidney donation	Number of transplantations with intraoperative stone management (no. successful treatment)	Technique	Procedure time (mean)	Stone size range (mean)	Stone location	Follow-up range (mean)	Complications in recipients	Complications in donors
Kumar[70]	2003	6	1 (1)	Small pyelotomy	N/A	N/A	N/A	0.3-7.4 yrs. (3.26 ± 0.6 yrs.)	None	None
Rashid[81]	2004	10	10 (9)	ExURS: 6 holmium laser, 3 basket	3-28 min. (6.5 min)	1-8 mm (5.2 mm)	3 upper pole, 3 mid pole, 4 lower pole	18-60 months for donor (33.2 months) 18-60 months for recipient (36.4 months)	None	None
Devasia[71]	2005	5	1 (1)	Nephrolithotomy	N/A	15 mm	1 lower pole	1-2 yrs.	None	None
Vasdev[80]	2011	5	3(3)	ExURS (n=1) and On- Table URS (n=2)	N/A	3-5 mm (3.6 mm)	1 mid pole, 2 lower pole	48-84 months (64 months)	None	None
Patel[76]	2011	10	3 (3)	ExURS (n=1) and in vivo URS (n=2)	N/A	N/A	N/A	24 months median	None	None
Schade[82]	2011	23	23 (17)	ExURS: 6 holmium laser, 12 basket	3-10 min. (6.2 min.)	2-6 mm (3.9 mm)	5 upper pole, 10 mid pole, 13 lower pole	63 ± 47.2 months median for recipient	1 (postoperative complete occlusion of the ureteroneocystotomy	N/A

TABLE 3. (Continued)

Author	Year	Number of stone forming donors proceeded with kidney donation	Number of transplantations with intraoperative stone management (no. successful treatment)	Technique	Procedure time (mean)	Stone size range (mean)	Stone location	Follow-up range (mean)	Complications in recipients	Complications in donors
Olsburgh[79]	2013	20	17 (10)	ExURS: 4 holmium laser, 5 basket, 1 laser and basket	10-45 min.	1-12 mm (3.2 mm)	5 upper pole, 5 interpolar, 7 lower pole	12-49 months for donors (26 months) 1-24 months CT/US imaging for recipient (10 months) + US at 37 month	None	None
Rizkala[78]	2013	54	1 (1)	ExURS: 1 basket	N/A	2 mm	N/A	22.5 months median for donors 47.4 months median recipient	None	None

N/A, not available

al. published the prevalence of kidney stones by CTA in potential donors was 4%, calculated during a period of 3.5 years.[84] In addition, they noticed that, in comparison with intraoperative findings, CTA has an accuracy rate of 93% in delineating vascular anatomy.

Another aspect that is still unknown is whether the clinical characteristics differ in patients with asymptomatic kidney stones. In 2011, Lorenz *et al.* determined whether risk factors and comorbidities among persons with asymptomatic kidney stones differ from clinical characteristics described in symptomatic kidney stone formers.[85] A total of 1,957 potential living donors were screened with CTA in eight years and 1,719 of them were unaffected subjects (group 1). 9.5% of the potential donors had only asymptomatic radiographic stones (group 2), whereas 2.7% of the potential donors had a history of symptomatic kidney stones (group 3). The prevalence of asymptomatic kidney stone formers was significant more likely to Caucasian race ($P<0.05$) and to have a 24h urine volume less than 1000ml ($P<0.05$). However, these groups were not characterized for other medical conditions.

COHORT ANALYSIS

Baseline characteristics

A total of 1,555 live donor nephrectomies were performed during a period of 21 years at our center (1994-2014). Of these, 36 (2.3%) live kidney donors had asymptomatic kidney stone(s) with a median stone size of 4.5mm and a median of one stone per kidney (range 1-3 stones). In addition, in two donors bilateral kidney stones were present. 75.5% of the stones were located in the mid or lower pole. Regarding the donor baseline characteristics, 55.6% was male and the median age of the donors was 55.4 years. Nine (25%) donors had a history of previous symptomatic kidney stone(s) with a median time of 9.5 years before transplantation. From the 36 donors with stones, 21 donors donated a stone-bearing kidney and 15 donated the contralateral kidney, while the kidney with stone(s) was left in situ. The motivations for this choice were because of vascular complexity, surgical preference or the well-considered choice to donate the healthy kidney. The baseline characteristics of these donors are summarized in Table 4.

The renal transplant recipients of these 36 live kidney donors had a median age of 42.8 years and 44.4% was male. Three (8.3%) recipients already had a history of symptomatic kidney stones in one of their native kidneys. Seventeen (47.2%) of these recipients received a pre-emptive transplantation. Table 5 summarizes the characteristics of the recipients.

Cohort analysis: outcome of transplantation of stone-bearing kidneys and their donors

In our cohort study, 21 stone-bearing kidney donations took place. The median follow-up time for donors was 5.08 years (range 0.08-12.17 years; Table 6). During follow-up, there were three (14.3%) stone-relating events in the donors. These consisted of two cases of renal colic due to newly formed kidney stones, which passed spontaneously without intervention. However, these donors had a history

TABLE 4. Baseline characteristics of live kidney donors with stones.

Donor characteristics	Live kidney donors with stones (n=36)	Transplantation of the stone-bearing kidney (n=21)	Transplantation of the non-stone bearing kidney with stones left *in situ* in contralateral kidney (n=15)
Gender (male; female)	20 (55.6%) 16 (44.4%)	12 (57.1%) 9 (42.9%)	8 (53.3%) 7 (46.7%)
Age (years)	55.37 [34.58-75.46]	53.3 [43.79-75.46]	60.25 [34.58-65.58]
ASA classification (I;II)	18 (52.9%) 16 (47.1%)	12 (63.2%) 7 (36.8%)	6 (40.0%) 9 (60.0%)
Body Mass Index (kg/m^2)	26.24 [18.90-35.76]	26.53 [18.90-34.09]	25.95 [20.80-35.76]
Symptomatic stone history (yes; no)	9 (25%) 27 (75%)	6 (28.6%) 15 (71.4%)	3 (20.0%) 12 (80.0%)
Time since stone history (years)	9.5 [1.5-30.0]	7.25 [1.5-30.0]	11.0 [2.0-15.0]
Scans (MRI; CT; MRI+CT; DSA+MAG3+ECHO; DSA+MAG3+ECHO+IVP)	12 (33.3%) 11 (30.6%) 7 (19.4%) 4 (11.1%) 2 (5.6%)	9 (42.9%) 6 (28.6%) 6 (28.6%) 0 (0%) 0 (0%)	3 (20.0%) 5 (33.3%) 1 (6.7%) 4 (26.7%) 2 (13.3%)
Stone laterality (right; left; bilateral)	16 (44.4%) 18 (50%) 2 (0.6%)	8 (38.1%) 11 (52.4%) 2 (9.5%)	8 (53.3%) 7 (46.7%) 0 (0%)
Number of stones	1 [1-3]	1 [1-3]	1 [1-3]
Stone size (mm)	4.5 [1-9]	4.0 [1.0-9.0]	5.0 [1.0-7.0]
Stone location (upper pole; midpole; lower pole; interpolar)	6 (12.2%) 13 (26.5%) 24 (49%) 6 (12.2%)	3 (9.4%) 7 (21.9%) 19 (59.3%) 3(9.4%)	3 (17.7%) 6 (35.3%) 5 (29.4%) 3 (17.7%)
Pre-op serum creatinine (µmol/L)	72.0 [54.0-103.0]	72.0 [57-103]	72.0 [54-90]
Pre-op serum eGFR (ml/min)	87.0 [62.0-90.0]	81.0 [63-90]	90.0 [62-90]
Kidney (left; right)	20 (55.6%) 16 (44.4%)	12 (57.1%) 9 (42.9%)	8 (53.3%) 7 (46.7%)

of previous symptomatic kidney stone(s). The other donor had a spontaneous passage of a kidney stone twice without any interventions.

The follow-up of the 21 recipients of these stone-bearing kidneys was 5.0 years (range 0-10.0 years; Table 7). During follow-up, only three complications occurred. One recipient developed an impaired kidney function due to the transplanted kidney stones three years postoperative. This was treated four times unsuccessfully with shockwave lithotripsy. Eventually, an open ureter re-implantation with stone evacuation was performed successfully. The second recipient developed an acute serum creatinine increase due to a distal ureter stone in the transplanted kidney. This was treated successfully with shockwave

TABLE 5. Baseline characteristics of renal transplant recipients receiving kidneys from live kidney donors with stones.

Recipient characteristics	All recipients (n=36)	Recipients receiving the stone-bearing kidney (n=21)	Recipients receiving the non-stone bearing kidney (n=15)
Gender (male; female)	16 (44.4%) 20 (55.6%)	8 (38.1%) 13 (61.9%)	8 (53.3%) 7 (46.7%)
Age (years)	42.82 [18.67-70.60]	48.17 [18.67-70.60]	38.92 [20.50-64.0]
ASA classification (II; III; IV)	10 (33.3%) 17 (56.7%) 3 (10.0%)	6 (33.3%) 9 (50.0%) 3 (16.7%)	4 (33.3%) 8 (66.7%) 0 (0%)
Body Mass Index (kg/m^2)	23.0 [17.56-37.18]	22.94 [17.56-34.85]	23.71 [18.58-37.18]
Relation (specified direct; specified indirect; unspecified)	27 (75%) 7 (19.4%) 2 (5.6%)	15 (71.4%) 4 (19.0%) 2 (9.5%)	12 (80.0%) 3 (20.0%) 0 (0%)
Pre-emptive transplantation (yes; no)	17 (47.2%) 19 (52.8%)	9 (42.8%) 12 (57.2%)	8 (53.3%) 7 (46.7%)
Symptomatic stone history (yes; no)	3 (8.3%) 33 (91.7%)	0 (0%) 21 (100%)	3 (20.0%) 12 (80.0%)
Pre-op serum creatinine (µmol/L)	525.0 [199.0-1637.0]	667.0 [199.0-1634.0]	521.0 [362.0-1637.0]
Fossa iliaca (left; right)	15 (41.7%) 21 (58.3%)	9 (42.9%) 12 (57.1%)	6 (40.0%) 9 (60.0%)

lithotripsy. The last recipient noticed a macroscopic hematuria, which occurred three years after transplantation. This also was successfully treated with the percutaneous nephrolithotomy technique.

Cohort analysis: Outcome of transplantation of non-stone bearing kidneys and their donors with stones left in situ in the contralateral kidney

There were fifteen donors who donated their non-stone bearing kidney in our study. In these donors, the median follow-up time was 7.5 years (range 0.08-19.17 years; Table 6). During follow-up only two events occurred. One donor developed an urosepsis seven years after transplantation due to an obstructing ureteral stone. This was first treated with antibiotics and a nephrostomy, followed with shockwave lithotripsy, which was unsuccessful. The stone was later removed successfully with a ureterorenoscopy. The other donor had three stones as seen on the screening, which were successfully treated with shockwave lithotripsy four years after donation.

The recipient had a median follow-up time of 6.5 years (range 0.17-20.08 years; Table 7). During the follow-up time, none of the recipients had any stone episodes or other stone-related adverse events.

DISCUSSION

In the past decades, living kidney donation has become increasingly important in the field of transplantation to increase the donor pool. There is a shift in accepting more and more extended criteria donors

TABLE 6. Intra- and postoperative outcome for live kidney donors with stones who donated either the stone-bearing or the non-stone bearing kidney.

	Live kidney donors with stones (n=36)	**Transplantation of the stone-bearing kidney (n=21)**	**Transplantation of the non-stone bearing kidney (n=15)**
Warm ischemia time (minutes)	3.0 [1.5-10]	3.0 [2.0-10.0]	3.0 [1.5-6.0]
Estimated blood loss (ml)	137.5 [0-2200]	110.0 [0-2200.0]	200.0 [0-750.0]
Skin-to-skin time (minutes)	189.0 [90.0-355.0]	205.0 [90.0-355.0]	158.0 [104.0-228.0]
Intraoperative complication rate (major; minor)	1 (2.8%) 8 (22.2%)	1 (4.8%) 5 (23.8%)	0 (0%) 3 (20.0%)
Postoperative complication rate (surgical; non-surgical)	2 (5.6%) 3 (8.3%)	0 (0%) 2 (9.5%)	2 (13.3%) 1 (6.7%)
Conversion to open technique	1 (2.8%)	1 (4.8%)	0 (0%)
Reoperation	0 (0%)	0 (0%)	0 (0%)
Postoperative length of stay (days)	3.0 [1.0-9.0]	3.0 [1.0-5.0]	4.0 [2.0-9.0]
Readmission	1 (2.8%)	1 (4.8%)	0 (0%)
Difference in serum creatinine[a] (µmol/L)	-38.0 [-84.0 - -19.0]	-38.0 [-84.0 - -19.0]	-42.0 [-66.0 - -26.0]
Difference in serum creatinine[a] (%)	-57.14% [-96.97 - -26.39]	-53.20% [-96.97 - -26.39]	-60.26% [-81.33 - -40.63]
Difference in serum eGFR[a] (mL/min)	31.0 [17.0-44.0]	31.0 [17.0-44.0]	31.5 [19.0-41.0]
Difference in serum eGFR[a] (%)	36.0% [23.29-54.32]	36.15% [23.29-54.32]	35.96% [27.78-48.75]
Difference in serum creatinine[b] (µmol/L)	-42.0 [-90.0 - -21.0]	-43.5 [-90.0 - -21.0]	-42.0 [-58.0 - -22.0]
Difference in serum creatinine[b] (%)	-58.61% [-114.49 - -29.13]	-56.61% [-114.49 - -29.13]	-58.91% [-81.03 - -40.28]
Difference in serum eGFR[b] (mL/min)	30.0 [17.0-45.0]	30.0 [17.0-45.0]	30.0 [18.0-41.0]
Difference in serum eGFR[b] (%)	36.71% [23.33-56.96]	36.48% [23.33-56.96]	36.71% [24.44-45.56]
Difference in serum creatinine[c] (µmol/L)	-40.0 [-92.0 - -16.0]	-42.0 [-92.0 - -21.0]	-37.0 [-72.0 - -16.0]
Difference in serum creatinine[c] (%)	-53.66% [-92.93 - -25.24]	-54.02% [-92.93 - -25.24]	-53.57% [-84.71 - -29.63]
Difference in serum eGFR[c] (mL/min)	29.0 [15.0-47.0]	28.5 [17.0-47.0]	29.0 [15.0-41.0]
Difference in serum eGFR[c] (%)	34.85% [16.67-59.49]	35.62 [23.33-59.49]	32.22% [16.67-51.25]
Difference in serum creatinine[d] (µmol/L)	-36.5 [-70.0 - -13.0]	-40.0 [-70.0 - 27.0]	-33.0 [-55.0 - -13.0]
Difference in serum creatinine[d] (%)	-50.35% [-85.94 - -24.07]	-52.44% [-74.24 - -27.18]	-47.92% [-85.94 - -24.07]
Difference in serum eGFR[d] (mL/min)	27.0 [12.0-38.0]	29.0 [17.0-38.0]	27.0 [12.0-34.0]
Difference in serum eGFR[d] (%)	34.62% [13.33-46.91]	37.24% [25.0-46.91]	31.82% [13.33-40.0]
Difference in serum creatinine[e] (µmol/L)	-31.0 [-69.0 - -11.0]	-36.0 [-69.0 - -18.0]	-29.5 [-45.0 - -11.0]
Difference in serum creatinine[e] (%)	-43.59% [-104.55 - -19.42]	-50.70% [-104.55 - -19.42]	-40.98% [-53.57 - -19.74]
Difference in serum eGFR[e] (mL/min)	28.0 [10.0-49.0]	28.0 [14.0-49.0]	24.0 [10.0-33.0]
Difference in serum eGFR[e] (%)	31.46% [11.11-56.79]	35.44% [20.59-56.79]	30.77% [11.11-38.67]
Stone-related complications during follow-up	5 (13.9%)	3 (14.3%)	2 (13.3%)
Follow-up time (years)	5.63 [0.08-19.17]	5.08 [0.08-12.17]	7.50 [0.08-19.17]

[a]: difference of serum creatinine/eGFR between the first day after surgery and preoperative values

[b]: difference of serum creatinine/eGFR between first month postoperative and preoperative values

[c]: difference of serum creatinine/eGFR between third month postoperative and preoperative values

[d]: difference of serum creatinine/eGFR between year one postoperative and preoperative values

[e]: difference of serum creatinine/eGFR between year five postoperative and preoperative values

TABLE 7. Intra- and postoperative outcome of patients receiving either stone-bearing or non-stone bearing kidneys.

	All recipients (n=36)	**Recipients receiving the stone-bearing kidney (n=21)**	**Recipients receiving the non-stone bearing kidney (n=15)**
2nd WIT (minutes)	22.0 [13.0-60.0]	22.0 [13.0-60.0]	20.5 [16.0-45.0]
Total warm ischemia time (minutes)	25.0 [18.0-70.0]	27.0 [18.0-70.0]	22.75 [19.0-31.0]
Estimated blood loss (ml)	350.0 [100.0-5000.0]	400.0 [100.0-5000.0]	300.0 [100.0-1000.0]
Skin to skin time (minutes)	128.0 [85.0-375.0]	132.5 [85.0-375.0]	116.0 [97.0-210.0]
Creatinine drop[a] (µmol/L)	271.5 [-54.0-851.0]	291.0 [48.0-851.0]	209.0 [-54.0 – 693.0]
Creatinine drop[a] (%)	45.81% [-5.28-84.84]	48.35% [16.39-84.84]	41.47% [-5.28 – 83.63]
Creatinine drop[b] (µmol/L)	377.50 [-1.0-1280.0]	393.0 [57.0-967.0]	347.0 [-1.0 – 1280.0]
Creatinine drop[b] (%)	75.03% [-0.10-93.24]	76.0% [9.47-91.94]	72.9% [-0.10 – 93.24]
Creatinine drop[c] (µmol/L)	438.0 [91.0-1467.0]	631.0 [91.0-1467.0]	382.0 [190.0-1439.0]
Creatinine drop[c] (%)	79.68% [45.73-90.77]	80.89% [45.73-90.77]	79.14% [48.10-89.15]
Creatinine drop[d] (µmol/L)	422.0 [202.0-1453.0]	530.5 [213.0-1453.0]	383.0 [202.0-1449.0]
Creatinine drop[d] (%)	76.16% [42.21-91.13]	75.48% [42.21-91.13]	76.64 [51.27-90.22]
Postoperative length of stay (days)	12.0 [5.0-166.0]	12.0 [7.0-166.0]	13.0 [5.0-50.0]
Readmission within 30 days	9 (25.0%)	4 (19.0%)	5 (33.3%)
Diuresis directly after reperfusion (yes; minimal; no)	31 (91.2%) 1 (2.9%) 2 (5.9%)	18 (94.7%) 0 (0%) 1 (5.3%)	13 (86.7%) 1 (6.7%) 1 (6.7%)
PCN	7 (19.4%)	4 (19.0%)	3 (20.0%)
DGF	1 (2.8%)	1 (4.8%)	0 (0%)
Urinary tract infection	9 (25.0%)	4 (19.0%)	5 (33.3%)
Urosepsis	4 (11.1%)	3 (14.3%)	1 (6.7%)
Rejection	5 (13.9%)	1 (4.8%)	4 (26.7%)
Graft lost	8 (22.9%)	5 (25.0%)	3 (20.0%)
Graft loss (months)	61.0 [1.0-84.0]	57.0 [1.0-73.0]	78.0 [20.0-84.0]
Transplantectomy	1 (2.8%)	1 (4.8%)	0 (0%)
Stone-related complications during follow-up	3 (8.3%)	3 (14.3%)	0 (0%)
Follow-up time (years)	5.58 [0-20.08]	5.0 [0-10.0]	6.5 [0.17-20.08]

[a]: difference of serum creatinine in recipients between the first day after surgery and preoperative values

[b]: difference of serum creatinine in recipients between first week postoperative and preoperative values

[c]: difference of serum creatinine in recipients between first month postoperative and preoperative values

[d]: difference of serum creatinine in recipients between year one postoperative and preoperative values

for living kidney donation.[8] Some transplant centers have loosened their donor inclusion criteria over the past decade because of the organ donor shortage.[86] Nevertheless, the transplant community should be extremely cautious when selecting a potential living donor for donation. The most important issue is

the safety of the potential live kidney donor. A live kidney donor is generally in good health and should not become a patient himself. Therefore, the risks and benefits of living kidney donation must clearly be discussed with both the potential donor and the recipient. Since the use of the high sensitive CTA scans, more asymptomatic kidney stones are incidentally detected in potential donors. These asymptomatic stones could possibly not be detected with the use of either intravenous pyelography or ultrasonography. Furthermore, during the pre-CTA era there may be some cases where kidneys with asymptomatic small stones are used inadvertently for donor nephrectomy.[79,83] Also, before the development of multiple minimally invasive treatments of kidney stones and the transition to the CTA, kidney stone disease was generally considered as an absolute contraindication to living kidney donation.[34] For transplant professionals, the task to find suitable donors while ensuring the safety of both donor and recipient could be difficult. Therefore, it becomes more interesting to accept potential donors with kidney stones. The use of stone-bearing living donor kidneys enhances legitimate concerns about the transplantation of kidneys with potentially harmful stones left *in situ* in the recipient, as well as the possibility of recurrence of stone disease in the donor. In the current guidelines and also described in this review, there is a difference in the criteria in accepting asymptomatic stone-bearing kidneys for donation. In addition, there is a lack of international consensus for potential stone-bearing kidney donors. In this systematic review, we found that there is a (major) difference in policies for donors with (a history of) kidney stone(s) between transplant centers.

In the literature, we observed a shift in trends and attitudes towards accepting stone-bearing live kidney donors in the United States and Europe (Germany).[68,69] Nevertheless, the most important cause for this shift is based on organ need, as long-term patient outcome and international consensus are lacking for this unique group of patients.

The different ways in which potential donors with asymptomatic kidney stone(s) *in situ* can be managed are as follows: 1) conservatively with adequate follow-up and monitoring; 2) treatment of the stone(s) before, during or after the transplantation. When these stone-bearing kidneys are conservatively managed, there often is a spontaneous passage in the recipient with no other side effects. Besides the allograft kidney is denervated in the recipient leaving no classic colic at presentation. However, the follow-up must be proper and the patient must be counseled accordingly in order to obtain optimal treatment under these circumstances. Furthermore, it is necessary for the transplant professionals to pay extra attention to and intervene upon adequate hydration (e.g., early treatment of diarrhea), early treatment of metabolic and urinary abnormalities during the early post-transplant period of the recipients of a stone-bearing allograft kidney. An another important aspect is that a kidney stone may cause an obstruction which can lead to kidney damage.[38] With regard to this, the preference should be to the stone-bearing kidney for donor nephrectomy because of the potential risk of obstruction from a stone in the solitary remaining kidney. Besides, transplant recipients are closely followed up by protocol so it is less likely to lose these recipients in the follow-up. However, the healthy live kidney donors can be lost easier during the follow-up.

The second option for the management of potential donors with asymptomatic kidney stone(s) is to treat them. Instead of pre- and postoperative treatment, nowadays ExURS treatment of the kidney stones could be applied during bench surgery before implantation. The ExURS treatment of kidney stones gives a lower incidence of (stone-associated) complications than other minimally invasive pre- and postoperative treatments (e.g., percutaneous nephrolithotomy, ureteroscopy, and shockwave lithotripsy). Furthermore, in the literature we observed promising results about the ExURS treatment of kidney stone(s). The ischemia time has an influence on the quality and function of the allograft kidney. Therefore, when performing ExURS the procedure time must be as short as possible. The literature states a short learning curve and the implantation of the surgery must occur in parallel or removing the kidney stones after revascularization (On-Table technique) to gain an advantage for ExURS treatment.[79,82]

On the other hand, in some cases CTA was 'too' sensitive causing false-positive scan results.[71,78,79] Upon further investigating these findings, there was an intraparenchymal calcification found in the kidney, which could be mistaken for kidney stones on CTA. It may also be a possibility of spontaneous passage of the asymptomatic kidney stone in the time period between the CTA assessment and transplantation. Nevertheless, with ureteroscopy all calyces of the kidney can be visualized and differentiation between stone and calcification can be made. This may be considered as an advantage for choosing the ExURS technique. Therefore, ExURS treatment could be considered among potential donors with suspicion for asymptomatic kidney stone(s).

The cohort of live kidney donors in the Erasmus MC consisted of 1,555 living kidney donations during a period of 21 years. The prevalence of asymptomatic stones in the literature ranged from 0.6% to 7%, but in our cohort analysis the prevalence was 2.3% (n=36). This could be an under interpretation because of false negative results of other preoperative imaging modalities than MRA and CTA. We would to stress that especially these extended criteria donors with kidney stones should be referred to a large tertiary transplant center/high volume center to ensure optimal donor safety.

Limitations

This systematic review has several limitations. Our findings support the inclusion of asymptomatic stone-bearing donors for living kidney donation regarding short-term follow-up. In the literature, the presented results about the outcome of asymptomatic stone-bearing living donor kidneys are promising. However, to date there is a lack of the long-term outcome (longer than 10 years) for these donors to confirm these outcomes. Furthermore, almost all studies who described the outcome of stone-bearing live kidney donors have several limitations, such as a retrospective study design, small sample size, and single-center experience. Therefore, the transplant community needs to be careful when delineating hard conclusions from these studies regarding asymptomatic stone-bearing living kidney donation.

Another issue that should be attended is that that most of the potential living donors have more than one extended criterion. Although an asymptomatic potential donor with a current (or a history of) kidney stone disease can safely proceed to living kidney donation, a combination of several extended

criteria may cause a problem regarding donor safety. Our conducted review did not reach any new insight in this important issue.

Also, the scoring of the evidence was performed through GRADE method. In our opinion, this is a great method scoring the level of evidence. Unfortunately, the quality of the included articles ranges from very low to low, which can be explained by the fact that our systematic review consists of observational studies, automatically downgrading the level of evidence.

Despite the limitations in current available literature, we conclude that a potential donor with (a history of) asymptomatic kidney stone(s) may be considered for living kidney donation. The risks and benefits of living kidney donation must clearly be discussed with both the potential donor and the recipient. Optimal guidance and counseling of donor and recipient with a sufficient long-term donor follow-up is very important. All potential kidney donors with asymptomatic kidney stone(s) should undergo a complete metabolic work-up, e.g., serum electrolyte values, chemistry panel, and 24-hour urine collection. If this careful work-up is completed in these potential donors with and shows no abnormal findings, the donor can safely donate his or her kidney.

Altogether, current guidelines are reluctant in statements to include potential donors with stone-bearing kidneys. However, by performing this first systematic review and cohort analysis regarding this topic, we hope to have given a better insight in the consequences of selecting donors with stone-bearing kidneys and that it is safe to include them, but that careful screening ought to be advocated, especially in these extended criteria donors.

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Chapter 10

Summary in English and Dutch

Chapter one provides the general introduction and aim and outline of this thesis, outlining several topics in the field of (live) kidney donation and transplantation. The increasing incidence of end-stage renal disease (ESRD) has led to an increase in the need for donor organs, as kidney transplantation remains the best treatment for these patients. However, the number of available kidneys from deceased donors cannot meet the demand. Luckily, a solution to this problem is live kidney donation, which has several advantages compared with deceased donation. Furthermore, for those who do not have a (suitable) live kidney donor, inventive programs for living kidney donation have been developed. Selection, screening and informed consent of live kidney donors is discussed, including so-called extended criteria live kidney donors. These consist of potential kidney donors with one or more defined comorbidities, such as overweight or obesity, hypertension, older age, vascular multiplicity, or stone-bearing kidneys. Also, women of childbearing age and minors as potential donors are in some centers considered as 'non-standard/extended' donors. Several of these criteria have been investigated in this thesis to give an overview of the outcome of these donors and obtain a definite answer whether or not they can safely be included to enlarge the donor pool.

Chapter two presents a systematic review carried out to combine current guidelines regarding extended criteria donors and all available literature in this field. Aim was to obtain insight in current ideas and practices about donors with older age, overweight and obesity, hypertension, vascular anomalies/multiplicity, nulliparous women, and minors as donors. 2,079 articles were reviewed as well as five major guidelines. Based on the analysis of the available guidelines, we conclude that there is no uniform approach regarding extended criteria donors. Statements about in- or exclusion of these types of donors remain rather vague, and are often of a subjective nature and not always evidence-based. Based on the literature search, live kidney donation in older donors (up to 70 years of age) seems to be safe as outcome is comparable to younger donors. Obese donors have comparable outcome to lean donors, in short- and mid-term follow-up. However, long-term follow up data are lacking. Since little literature is available proving the safety of donation of hypertensive donors, caution is advised, but donors with up to two antihypertensive drugs can be safely included. Vascular multiplicity poses no direct danger to the donor and women of childbearing age can be safely included as donors. Although outcome after donation in minors is shown to be comparable to adult donors, they should only be considered if no other options exist. In summary, we conclude that the analyzed factors above should not be considered as absolute contraindications for live kidney donation.

We have carried out an online survey on the current attitudes of transplant professionals regarding extended donor criteria, which is presented in **chapter three**. An online survey was sent to 1,128 European Society for Transplantation members. The questionnaire consisted of two parts; an objective part asking for center policies regarding acceptance of extended criteria live kidney donors, and a subjective part for transplant surgeons, regarding their personal opinions in this matter. Questions were included about several extended donor criteria, such as overweight and obesity, age limit, vascular multiplic-

ity, minors as donors, and comorbidities like hypertension, impaired fasting glucose, kidney stones, malignancies and renal cysts. Furthermore, questions about preoperative imaging, multidisciplinary team discussions and operative techniques were included. Significant differences exist between regions in Europe in acceptance of donors with several extended criteria. Furthermore, differences are seen regarding preoperative work-up, both in screening specialists as in preoperative imaging. Remarkably, almost a quarter of transplant professionals sometimes deviate from their center policy, resulting in more or less comparable personal beliefs regarding extended criteria. Furthermore, if center volume is smaller, transplant professionals are more reluctant in accepting these kinds of donors. Interestingly, in 9.7% of the transplant centers, potential live kidney donors are not discussed in a multidisciplinary team. In these cases, only a transplant surgeon or nephrologist decides if the potential donor should be accepted. Laparoscopic transperitoneal donor nephrectomy is most practiced around the world as live kidney donation technique. By performing this survey amongst a large group of transplant professionals in Europe and other countries around the world, we gained insight in both center policies as well as personal opinions of acceptance of extended criteria donors. Variety is seen in center policies as well as personal attitudes, proving the need for a uniform guideline, that gives a clear advice regarding the in- or exclusion of these extended criteria donors.

Chapter four describes a systematic review carried out to reveal current practices regarding the informed consent procedure for live kidney donors around the world in order to gain more insight in this procedure, to eventually be able to optimize and standardize the informed consent procedure. Based on the systematic literature search procedures vary greatly between centers and transplant professionals vary in information they disclose. Although research has demonstrated that donors often make their decision based on moral reasoning rather than balancing risks and benefits, providing them with accurate, uniform information remains crucial, as donors report feeling misinformed about or unprepared for donation. Although a standardized procedure may not provide the ultimate solution, it is vital to minimize differences in live donor education between transplant centers. We conclude that there is a definite need for guidelines on how to provide information and obtain informed consent from live kidney donors, to assist the transplant community in optimally preparing potential donors.

In **chapter five,** we present a systematic review and meta-analysis on the relation between body mass index (BMI) and outcome of laparoscopic donor nephrectomy. A BMI above 35 is generally considered a relative contraindication for donation. After screening and selection, fourteen studies were identified and reviewed. Eight perioperative donor outcome measures were meta-analyzed; operation duration, conversion from laparoscopic donor nephrectomy to an open procedure, warm ischemia time, estimated blood loss, length of hospital stay, perioperative complications, difference in serum creatinine and difference in estimated glomerular filtration rate (GFR). Three of these outcome measurements demonstrated significant differences in favor of low BMI (<30) donors: mean difference in operation duration, mean difference in rise in serum creatinine, and risk ratio for conversion. In the other five,

no significant differences were found between groups. Most importantly, the rate of perioperative complications (which is often adduced as reason to decline a high BMI donor) was not higher if donor BMI was higher than 30. Therefore, we conclude that a high BMI alone is no contraindication for live kidney donation regarding short-term outcome. However, long-term follow-up of these donors should be established, in order to ensure donor safety over an extended period of time.

As can be concluded from chapter five, the BMI is not an optimal parameter for predicting outcome after live donor nephrectomy. **Chapter six** describes a retrospective study we carried out in the cohort of live kidney donors in the Erasmus MC from 2004 until 2013 assessing the role of perirenal- and intra-abdominal fat mass. From 620 donors, preoperative abdominal CT or MR imaging was available. Automated volumetric measurement of the amount of perirenal fat in mm^3 was carried out on CT-scans. As a validation, several linear measurements of abdominal visceral fat (IAF-measurements) were performed on both CTA (-as MRA-scans). These data were correlated with several outcome measures of laparoscopic donor nephrectomy in both univariable and multivariable regression models. As we already hypothesised, the BMI correlates with some outcome measures of laparoscopic donor nephrectomy. However, the volume of perirenal fat demonstrated a stronger correlation in even more outcome measures in univariable and multivariable regression: operation duration, estimated blood loss and difference in serum creatinine and estimated GFR at one year after donation. Furthermore, the IAF-measurements show the same significant correlation, both in the CT-cohort as in the MRI-cohort. Therefore, it is confirmed that the BMI alone is not the best predictor for outcome of laparoscopic donor nephrectomy. Moreover, donor BMI has no correlation with outcome of renal transplant recipients. In our opinion, the measurement of intra-abdominal fat could be a useful additional parameter in predicting peri- and postoperative outcome of laparoscopic donor nephrectomy and should be included in the assessment of possible live kidney donors.

As not only outcome of live kidney donors is important, we were interested in outcome of renal transplant recipients as well. In **chapter seven,** we describe the role of the BMI in recipients, based on a systematic review and meta-analysis. After identifying 5,526 studies addressing this topic, 56 studies were included, including data of more than 209,000 renal transplant recipients. The majority of the outcome measures showed significant difference in favor of recipients with a BMI below 30. Both perioperative outcome measures (wound infection, dehiscence and incisional hernias), as delayed graft function (DGF) and acute rejection occurred more often in high BMI recipients. Furthermore, graft- and patient survival was impaired in these recipients, at least up to three years after transplantation. Most important, high BMI recipients had a 1.5 higher chance of dying within a couple years after transplantation. Therefore, we postulate that ESRD patients with a BMI above 30 preferably should lose weight prior to renal transplantation. If this cannot be achieved with common measures, in morbidly obese renal transplant candidates, bariatric surgery should be considered. However, the transplant community needs to real-

ize that even obese renal transplant recipients have a significant survival benefit from transplantation despite the reduced risk of death of obese dialysis patients.

Chapter eight discusses donor kidneys with vascular multiplicity. As it is thought that donating a kidney with complex anatomy has an increased risk of complications, for both the donor as the recipient, we performed an analysis of the prevalence of vascular multiplicity in the cohort of the Erasmus MC, from 2006 to 2013. Vascular anatomy as imaged by MRA, CTA, or other modalities was compared with intraoperative findings. Furthermore, the influence of vascular multiplicity on outcome of donors and recipients was studied. In 237 donors, vascular multiplicity was present (25% compared with 18-20% worldwide). CTA had the highest accuracy levels regarding vascular anatomy assessment. Regarding outcome of donors with vascular multiplicity, warm ischemia time and skin-to-skin time were significantly longer if arterial multiplicity was present. Skin-to-skin time was significantly longer and complication-rates (Clavien-Dindo Grade I) were higher in donors with venous multiplicity. Outcome of renal transplant recipients showed a significantly increased warm ischemia time, higher rate of DGF and lower rate of biopsy-proven acute rejection in patients receiving a kidney with arterial multiplicity compared with kidneys with singular anatomy. However, it should be noted that these outcome measures are of relatively low clinical value. Most importantly, graft- and patient survival was not worse in recipients of a kidney with vascular multiplicity. We conclude that vascular multiplicity should not be a contraindication, since it has little impact on clinical outcome in the donor as well as in renal transplant recipients.

In **chapter nine** we present a systematic review about the prevalence of kidney stones (nephrolithiasis) amongst live kidney donors and a cohort analysis of the live donors that have donated between 1994 and 2014 (n=1,555) in the Erasmus MC. Since little is known about the presence of kidney stones in live kidney donors and transplanted donor kidneys, we aimed to retrieve more insight in this matter. Guidelines state that nephrolithiasis is at least a relative contraindication to live donor nephrectomy because of the future risk that recurrent stones, obstructions, and infections will injure the remaining kidney. In addition, nephrolithiasis not only places the donor at risk; inadvertent transplantation of a kidney with stones could also impair recipient outcome. The prevalence of kidney stones in live kidney donors in the literature ranges from 0.6% to 7%. In our cohort, the prevalence of kidney stones was 2.3% (36 live kidney donors). In our cohort, there were some complications regarding the presence of stones in recipients, but all were successfully treated. Most importantly, graft survival was not worse compared with transplantation of non-stone bearing kidneys. Of the fifteen donors that donated a non-stone bearing kidney and had stones in situ in the contralateral kidney, two were treated successfully for stone-relating issues after donor nephrectomy. Based on the available literature and the cohort analysis, it seems that transplantation of stone-bearing kidneys is safe. Furthermore, reported outcome of live kidney donors with one or more stones in the non-donated kidney is excellent. Guidelines should be updated, stating that potential live kidney donors with stones should not on forehand be excluded for donation.

In **hoofdstuk één** wordt een overzicht gegeven van de opzet van het proefschrift, waarbij verschillende topics op het gebied van nierdonatie bij leven en transplantatie worden uitgelicht. De toenemende incidentie van eindstadium nierfalen heeft geleid tot een toename van de noodzaak voor donororganen, aangezien niertransplantatie de beste behandeling blijft voor deze groep patiënten. Helaas kan het aantal beschikbare nieren van overleden donoren het tekort niet opvullen. Gelukkig is nierdonatie bij leven een oplossing voor dit probleem. Dit heeft verschillende voordelen ten opzichte van donatie na de dood. Bovendien, voor de patiënten die geen (geschikte) levende donor hebben, zijn er verschillende inventieve programma's ontwikkeld. Selectie, screening en informed consent van levende nierdonoren worden besproken, inclusief de zogenaamde 'extended criteria' levende nierdonoren. Deze bestaan uit potentiële nierdonoren met een of meer comorbiditeiten, zoals overgewicht of obesitas, hypertensie, hogere leeftijd, meerdere bloedvaten van de nieren, of de aanwezigheid van nierstenen. Verder worden vrouwen in de vruchtbare leeftijd en jongeren (onder de 18) in sommige transplantatiecentra beschouwd als 'geen-standaard/extended' donoren. Verschillende van deze criteria zijn onderzocht in dit proefschrift om een overzicht van de uitkomsten van deze donoren te geven en om een definitief antwoord te vinden of deze groep veilig geïncludeerd kan worden om de donorpool te vergroten.

Hoofdstuk twee beschrijft een systematische review die uitgevoerd is om de huidige richtlijnen over extended criteria donoren en de literatuur op dit gebied te combineren. Het doel was om inzicht te krijgen in de huidige opvattingen over donoren van hogere leeftijd, met overgewicht of obesitas, hypertensie, afwijkende anatomie van de bloedvaten van de nier, vrouwen in de vruchtbare leeftijd en jongeren als potentiële donoren. 2079 artikelen zijn beoordeeld, evenals vijf grote richtlijnen. Op basis van de analyse van de beschikbare richtlijnen, concluderen we dat er geen uniforme benadering is betreffende extended criteria donoren. Stellingen over in- of exclusie van deze donoren blijven vaag, en zijn vaak van subjectieve aard en niet altijd gebaseerd op wetenschappelijk onderzoek. Op basis van de analyse van de literatuur is nierdonatie bij leven bij oudere donoren (tot de leeftijd van 70 jaar) veilig aangezien uitkomsten vergelijkbaar zijn met die van jongere donoren. Donoren met obesitas hebben ook vergelijkbare uitkomsten ten opzichte van slankere donoren, in korte- en medio duur van follow-up. Echter, lange-termijn data ontbreken. Aangezien er weinig literatuur beschikbaar is die de veiligheid bewijst van donatie van donors met hypertensie is voorzichtigheid geboden. Donoren met maximaal twee antihypertensiva kunnen echter veilig worden geïncludeerd. De aanwezigheid van meerdere bloedvaten van de nier is niet direct schadelijk voor de donor en vrouwen in de vruchtbare leeftijd kunnen ook veilig geïncludeerd worden als donor. Alhoewel uitkomsten na donatie van jongeren vergelijkbaar zijn met volwassen donoren, moet deze groep alleen beschouwd worden als potentiële donor als er geen andere opties zijn. Samenvattend concluderen we dat de geanalyseerde factoren die hierboven genoemd zijn niet beschouwd moeten worden als absolute contra-indicatie voor nierdonatie bij leven.

We hebben een online enquête uitgevoerd naar de huidige mening van transplantatieprofessionals voor wat betreft extended donor criteria, welke wordt gepresenteerd in **hoofdstuk drie**. Een online

enquête is verstuurd naar 1128 leden van de European Society for Transplantation. De vragenlijst bestond uit twee delen; een 'objectief' deel dat betrekking had op het centrum beleid ten aanzien van de aanvaarding van extended criteria nierdonoren, en een 'subjectief' deel voor transplantatiechirurgen, met betrekking tot hun persoonlijke ervaringen en meningen betreffende dit onderwerp. Vragen werden opgenomen over diverse extended donor criteria, zoals overgewicht en obesitas, leeftijdsgrens, de aanwezigheid van meerdere bloedvaten van de nieren, minderjarigen als donoren en comorbiditeiten zoals hoge bloeddruk, een afwijkend glucosegehalte, nierstenen, maligniteiten en niercysten. Verder zijn er vragen opgenomen over preoperatieve beeldvorming, multidisciplinaire teamdiscussies en operatietechnieken. Er werden significante verschillen gevonden tussen de regio's in Europa in de aanvaarding van donoren met diverse extended criteria. Bovendien werd waargenomen dat er verschillen bestaan over preoperatieve voorbereiding, zowel in specialisten die donoren screenen als in preoperatieve beeldvorming. Opmerkelijk is dat bijna een kwart van de transplantatieprofessionals soms afwijkt van hun centrumbeleid, en dat er min of meer vergelijkbare persoonlijke overtuigingen zijn met betrekking tot extended criteria. Verder wordt er gezien dat wanneer het centrumvolume kleiner is, de transplantatieprofessionals meer terughoudend zijn in het accepteren van dit type donoren. Interessant is dat in 9.7% van de transplantatiecentra, potentiële levende nierdonoren niet in een multidisciplinair team besproken worden. In deze gevallen beslist slechts alleen een transplantatiechirurg of nefroloog of de potentiële donor wordt geaccepteerd. Laparoscopische transperitoneale donornefrectomie wordt het meest beoefend in de hele wereld als operatietechniek voor levende nierdonoren. Door het uitvoeren van dit onderzoek onder een grote groep van transplantatieprofessionals in Europa en andere landen van de wereld, hebben we inzicht gekregen in zowel het centrumbeleid als persoonlijke meningen van aanvaarding van extended criteria donoren. Op beide gebieden worden er verschillen gezien, waaruit blijkt dat er een uniforme richtlijn noodzakelijk is, die een duidelijk advies geeft over de in- dan wel exclusie van extended criteria donoren.

Hoofdstuk vier beschrijft een systematische review, dat werd uitgevoerd om de huidige praktijken te onthullen over de informed consent procedure voor levende nierdonoren wereldwijd, met het doel om deze uiteindelijk te kunnen optimaliseren en standaardiseren. Op basis van het systematisch literatuuronderzoek zien we dat procedures sterk variëren tussen de centra en dat transplantatieprofessionals variëren in informatie die ze verstrekken. Hoewel onderzoek heeft aangetoond dat de donoren vaak hun besluit nemen op grond van morele overwegingen in plaats van op de afweging tussen risico's en voordelen, blijft het van cruciaal belang om ze te voorzien van nauwkeurige, uniforme informatie. Dit is temeer van belang omdat donoren in enkele gevallen hebben gerapporteerd dat ze niet goed geïnformeerd of voorbereid zijn voorafgaand aan de donatie. Hoewel een gestandaardiseerde procedure niet automatisch de beste oplossing is, blijft het essentieel om de verschillen in educatie van levende donoren tussen transplantatiecentra te minimaliseren. We concluderen dat er een duidelijke behoefte is aan richtlijnen over hoe informatie te verstrekken en informed consent te verkrijgen van levende

nierdonoren, om transplantatieprofessionals te helpen bij het optimaal voorbereiden van potentiële donoren.

In **hoofdstuk vijf**, presenteren we een systematische review en meta-analyse over de relatie tussen de body mass index (BMI) en de resultaten van laparoscopische donornefrectomie. Een BMI boven 35 wordt algemeen beschouwd als een relatieve contra-indicatie voor donatie. Na screening en selectie van de artikelen, werden er uiteindelijk veertien studies geïncludeerd en beoordeeld. Acht perioperatieve uitkomstmaten van donoren werden gebruikt voor de meta-analyse; operatieduur, conversie van laparoscopische donornefrectomie naar een open procedure, warme ischemietijd, geschat bloedverlies, opnameduur, perioperatieve complicaties, verschil in serum creatinine en verschil in geschatte glomerulaire filtratiesnelheid (GFR). Drie van deze uitkomstmaten toonden significante verschillen in het voordeel van lage BMI (<30) donoren: gemiddeld verschil in operatieduur, gemiddeld verschil in stijging in serum creatinine, en risicoverhouding voor conversie. In de andere vijf uitkomstmaten, werden er geen significante verschillen gevonden tussen de groepen. Wat voornamelijk van belang is, is dat het aantal perioperatieve complicaties (welke vaak wordt aangevoerd als reden om een hoge BMI donor te weigeren) niet hoger waren bij donoren met een BMI hoger dan 30. We concluderen dat een hoge BMI op zichzelf geen contra-indicatie is voor nierdonatie bij leven, op basis van korte termijn resultaten. Lange termijn follow-up moet echter eerst bekend zijn om de veiligheid van donoren te kunnen garanderen.

Zoals uit hoofdstuk vijf kan worden geconcludeerd, is de BMI geen optimale parameter voor het voorspellen van de uitkomst na nierdonatie bij leven. **Hoofdstuk zes** beschrijft een retrospectieve studie die we hebben uitgevoerd in het cohort van levende nierdonoren in het Erasmus MC vanaf 2004 tot 2013, waarbij de rol van perirenale en intra-abdominale vetmassa is beoordeeld. Van 620 donoren, was er een preoperatieve abdominale CT- of MRI-scan beschikbaar. Op basis van de CT-scans werden er volumetrieën uitgevoerd van de hoeveelheid perirenaal vet in mm^3. Als validatie werden verschillende lineaire metingen van abdominaal visceraal vet (IAF-metingen) uitgevoerd op zowel CTA- als MRA-scans. Deze gegevens werden gecorreleerd met verschillende uitkomstmaten van laparoscopische donornefrectomie in zowel univariabele en multivariabele regressie modellen. Zoals we al verwachtten, correleert de BMI met een aantal uitkomstmaten van laparoscopische donornefrectomie. Echter, het volume van perirenaal vet toonde een sterkere correlatie met nog meer uitkomstmaten in univariabele en multivariabele regressie: operatieduur, geschat bloedverlies en verschil in serum creatinine en de geschatte GFR op een jaar na de donatie. Bovendien tonen de IAF-metingen dezelfde significante correlatie, zowel in het CT-cohort als in het MRI-cohort. Hiermee hebben we bevestigd dat de BMI op zichzelf niet de beste voorspeller is voor uitkomsten na laparoscopische donornefrectomie. Bovendien heeft donor BMI geen correlatie met de uitkomsten van niertransplantatiepatiënten. Naar onze mening zou de meting van intra-abdominaal vet een nuttige extra parameter kunnen zijn in het voorspellen van

de peri- en postoperatieve uitkomsten van laparoscopische donornefrectomie en moet deze worden opgenomen in de beoordeling van potentiële levende nierdonoren.

Omdat niet alleen goede uitkomsten van levende nierdonoren belangrijk zijn, hebben we ook gekeken naar de resultaten na niertransplantatie van ontvangers met een hoge BMI. In **hoofdstuk zeven**, beschrijven we de rol van de BMI bij deze patiënten, op basis van een systematische review en meta-analyse. Na het identificeren van 5526 artikelen over dit onderwerp, werden er zesenvijftig studies geïncludeerd, met gegevens van meer dan 209.000 niertransplantatiepatiënten. De meerderheid van de uitkomstmaten toonde significante verschillen in het voordeel van ontvangers met een BMI onder de 30. Zowel perioperatieve uitkomstmaten (zoals wondinfectie, wonddehiscentie en littekenbreuken), als delayed graft function en acute afstoting kwam vaker voor bij ontvangers met een hoge BMI. Verder was overleving van het orgaan en de ontvangers minder lang in deze groep, ten minste tot drie jaar na de transplantatie. Ontvangers met een hoge BMI hadden zelfs een anderhalf keer zo hoge kans om te overlijden binnen een paar jaar na de transplantatie. We stellen daarom dat patiënten die lijden aan eindstadium nierfalen met een BMI boven de 30 moeten afvallen voor een niertransplantatie. Indien dit niet kan worden bereikt met de gebruikelijke maatregelen, en zeker in het geval van morbide obesitas, zou bariatrische chirurgie overwogen moeten worden. Transplantatie professionals moeten echter beseffen dat zelfs niertransplantatiepatiënten met obesitas een significant overlevingsvoordeel van transplantatie hebben ondanks het verminderde risico op overlijden van obese dialysepatiënten ten opzichte van dialysepatiënten zonder obesitas.

Hoofdstuk acht bespreekt donornieren met meerdere nier(slag)aders. Aangezien er gedacht wordt dat het doneren van een nier met complexe anatomie een verhoogd risico heeft op het optreden van complicaties (voor zowel de donor als de ontvanger) hebben we een analyse uitgevoerd van de prevalentie van deze anatomie in het cohort van het Erasmus MC van 2006 tot 2013. Vasculaire anatomie zoals afgebeeld door MRA, CTA of andere modaliteiten werd vergeleken met intra-operatieve bevindingen. Hiernaast is er ook gekeken naar de invloed van meervoudige anatomie op de uitkomsten van donoren en ontvangers. Bij 237 donoren was meervoudige anatomie aanwezig (25% in vergelijking met 18-20% wereldwijd). CTA had de hoogste nauwkeurigheid voor wat betreft de weergave van de vasculaire anatomie preoperatief. Wat betreft de uitkomsten van donoren met meervoudige anatomie, waren warme ischemie tijd en skin-to-skin tijd significant langer als de nier meerdere nierarteriën had. Skin-to-skin tijd was significant langer en het aantal complicaties (Clavien-Dindo Graad I) was hoger bij donoren met meerdere niervenen. Uitkomsten van niertransplantatiepatiënten toonden een significant verhoogde warme ischemie tijd, hogere incidentie van delayed graft function en lagere incidentie van acute afstoting (met biopsie bewezen) bij patiënten die een nier met meerdere arteriën ontvingen ten opzichte van nieren met enkelvoudige anatomie. Er moet echter worden opgemerkt dat deze uitkomstmaten van relatief lage klinische waarde zijn, aangezien overleving van het orgaan en de patiënt niet slechter was bij ontvangers van een nier met meervoudige anatomie. We concluderen dat meervoudige

anatomie niet beschouwd moet worden als contra-indicatie, aangezien het weinig invloed heeft op de klinische resultaten bij zowel de donor als bij niertransplantatiepatiënten.

In **hoofdstuk negen** presenteren we een systematische review over de prevalentie van nierstenen (nephrolithiasis) onder levende nierdonoren en een cohortanalyse van levende nierdonoren die gedoneerd hebben tussen 1994 en 2014 (n=1555) in het Erasmus MC. Omdat er weinig bekend is over de aanwezigheid van nierstenen in levende nierdonoren en donornieren, hebben we geprobeerd om meer inzicht te krijgen betreffende dit onderwerp. In de huidige richtlijnen staat dat nephrolithiasis ten minste beschouwd moet worden als een relatieve contra-indicatie voor donornefrectomie vanwege het toekomstig risico op een recidief, obstructies, en infecties van de nier die achterblijft in de donor. Daarnaast is nephrolithiasis niet alleen een potentieel gevaar voor de donor; onbedoelde transplantatie van een nier met stenen zou ook de uitkomsten van de ontvanger kunnen benadelen. De prevalentie van nierstenen in levende nierdonoren in de literatuur varieert van 0.6% - 7%. In ons cohort was de prevalentie van nierstenen 2.3% (36 levende nierdonoren). De enkele complicaties die optraden bij ontvangers in ons cohort door nierstenen werden succesvol behandeld. Transplantaatoverleving was niet slechter ten opzichte van transplantatie van nieren zonder nierstenen. Van de vijftien donoren die een nier hadden gedoneerd zonder nierstenen, maar die wel één of meerdere stenen hadden in de contralaterale nier die achterbleef, traden er in slechts twee gevallen complicaties op die met succes werden behandeld. Op basis van de beschikbare literatuur en de cohortanalyse blijkt dat transplantatie van nieren met stenen veilig is. Bovendien zijn de resultaten van levende nierdonoren met één of meer stenen in de niet gedoneerde nier, uitstekend. We zijn van mening dat de richtlijnen moeten worden bijgewerkt, zodat potentiële levende nierdonoren met stenen op voorhand niet moeten worden uitgesloten van donatie.

Chapter 11

General discussion and future perspectives

With the rising incidence and prevalence of ESRD, the organ shortage of donor kidneys is a growing problem. Luckily, live kidney donation has already proven to successfully increase the donor pool. However, it still cannot meet the demand for donor kidneys. Several creative programs have been developed over the years, enlarging the numbers of transplantations even further. As the transplant community is still searching for possibilities to further expand live donation, the inclusion of extended criteria live kidney donors is an increasing phenomenon. Although short-term follow-up of these types of donors show good outcome, recent literature indicates that the long-term impact on renal function and vascular disease might be worse than previous studies reveal.[1,2] The authors state that live kidney donors are a highly selected group of healthy individuals and therefore cannot be compared with the general population. When outcomes are compared with a group of matched individuals who would have been eligible for donation, but did not donate, hazard ratio for all-cause death, cardiovascular death and the risk of ESRD was significantly increased. Although the control groups were not perfectly matched, transplant professionals should not underestimate the potential risks for a live kidney donor, especially in case of an extended criteria donor.

ATTITUDES AND INFORMED CONSENT

By performing an online survey amongst ESOT members, our hypothesis is confirmed that transplant professionals do not always comply with their respective strict center criteria regarding the inclusion of extended criteria donors. A quarter of the respondents replied that they sometimes deviate from center policy regarding extended criteria donors. This proves that screening of a potential live kidney requires an individual approach and that current policies may not be applicable to every potential donor. Furthermore, in line with the previously mentioned issue, the informed consent procedure also varies between transplant centers. Transplant professionals should provide potential donors with accurate, uniform information, as donors report feeling misinformed about or unprepared for donation.[3] Therefore, it is vital to minimize differences in live donor education between transplant centers. A uniform international informed consent procedure could be a useful addition in optimizing this process. For extended criteria donors, a specific informed consent procedure including the latest data, knowledge and risks on specific complications, could be of help to fully inform and prepare a potential donor.

EXTENDED DONOR CRITERIA

Although several guidelines exist regarding live kidney donation and the selection of potential (extended criteria) donors, no real hard statements or recommendations are made, and more importantly, not all transplant centers or professionals follow these guidelines. Thus, there is no uniform approach regarding these donors. By performing the studies as described in this thesis, we have obtained more insight on how to approach extended criteria donors.

Regarding older donor age, we state that biological age is more important than actual age. It should be noted that with increasing age, intuitively, transplant professionals are more reluctant in accepting

extended criteria donors to prevent ESRD in these donors. However, the incidence of ESRD in older individuals is lower, as the slope of kidney failure is less steep. Furthermore, the *a priori* life expectancy is lower. Next to the good results of kidney grafts from older donors, for the aforementioned reasons this group might be perfectly suitable for donation. Besides, previous studies in our center showed that older live kidney donors report an excellent quality of life and their body and cosmesis scores are high.[4,5]

As the worldwide incidence and prevalence of overweight and obese individuals will continue to rise, the transplant community will be confronted with potential overweight or obese donors. Based on our extensive review and meta-analysis, we state that (based on short-term follow-up) these donors can safely be included, primarily because perioperative complications do not occur more often in this group (in contrast to literature regarding other procedures in obese patients[6]). As we did not have much specific data regarding morbidly obese (BMI >35) potential live kidney donors, in our opinion, they should be advised to loose weight prior to donation. When conventional methods fail, bariatric surgery could be considered, in line with current bariatric surgery guidelines for non-donors. In general, every person, potential live kidney donor or not, with a BMI >40 or >35 with comorbidities, should be referred to a bariatric center.[7]

Since the BMI appears not to be a useful parameter in preoperative screening of live kidney donors, the role of linear measurements of intra-abdominal and volumetric measurements of perirenal fat on CT-scans was investigated. Previous studies showed potential correlation of linear measurements and outcome, and therefore we decided to investigate this concept using three-dimensional methods.[8] We conclude that aforementioned parameters have a stronger correlation with outcome after laparoscopic donor nephrectomy and could therefore be used as an addition during the donor screening. Ideally, a model should be created, combining both BMI and intra-abdominal fat to calculate peri- and postoperative risks for the donor. In the current era of tailor-made surgical approaches[9,10] and since donor nephrectomy in obese donors sometimes can be a surgical challenge, the hand-assisted retroperitoneoscopic (or laparoscopic) donor nephrectomy might be an easier technique in obese donors.

Hypertension should remain a relative contraindication for live kidney donation. Hypertensive live kidney donors with a blood pressure of approximately 140/90mmHg, established by 24-h ambulatory blood pressure measurement and normal renal function, show similar postdonation blood pressure and renal function as normotensive living kidney donors.[11] However, based on the evidence available, the exact degree of hypertension and renal function has not yet been established. In general, the manageability of the hypertension, the presence of other comorbidities, and overall health determine whether individuals with hypertension should be included or excluded as live kidney donors. It should be noted that antihypertensive treatment should be state-of-the-art before a potential donor is rejected. Furthermore, normotension established with up to two antihypertensive drugs is considered safe, in general. However, long-term data of this specific group is lacking. These conclusions are also in accordance with

the consensus guidelines that were adopted at the Amsterdam Forum in 2004, further stressing the importance of observing these donors among transplant centers.

Women of childbearing age or more specific nulliparous women are a specific group that can obviously not be labeled as 'extended criterion'. The discussion is in this case not related to the outcome of the donor nephrectomy but to the outcome of an eventual future pregnancy. Remarkably, although there is little literature available specifically investigating these potential donors,[12,13] current guidelines state that it is safe to include women of childbearing age for donation. However, recent literature states that gestational hypertension or preeclampsia was more common among living kidney donors than among healthy matched non-donors (odds ratio 2.4).[14] Although this study was of a retrospective nature, the control group was matched adequately consisting of healthy non-donors, who probably would have been eligible for donation. However, as the women in the control group were not screened as a potential donor would have been, this could lead to a bias in the analysis. Moreover, data of blood pressure, renal function, BMI and race was not available. Nonetheless, in our opinion, the effects of donation on maternal and fetal outcomes should be part of the routine discussion about the risks of donation during the informed consent procedure.

Guidelines state that minors (younger than 18 years of age) should not be considered as potential donors.[15] This seems in contradiction with the literature, as pediatric donors perform excellent, even in long-term (~30 years) follow-up.[16] The reason for this attitude lies logically in the great ethical discussion that is embedded within pediatric donation. One can argue if the limit should be set on 18 years, as minors from a certain age could be perfectly capable to make an informed decision in contrast to some individuals of >18years old. However, in our opinion, minors should only be considered if all other possibilities are explored and no other options exist.

Since we did not only want to focus on donors, but on renal transplant recipients as well, we investigated the role of the BMI and outcome after kidney transplantation. In contrast to the donors, a high BMI does have a negative influence on outcome after transplantation.[17,18] As in any overweight or obese person, risks of surgical complications such as wound infections, dehiscence and incisional hernias are higher. Especially, immunocompromised patients are at increased risk for these complications. As a consequence, in our opinion, every patient with an impaired renal function with a BMI above 30 should lose weight prior to transplantation, preferably several years before the kidney disease progresses into ESRD. If common measures for weight loss fail, bariatric surgery should be considered if the BMI is 35 or higher. We know that in the general population morbidly obese individuals with a BMI of higher than 40 or 35 with comorbidities greatly benefit from bariatric surgery. Although even with bariatric surgery, a BMI below 30 might not be achieved, based on the results of our studies, we hypothesize that any weight loss will contribute to better outcome after transplantation. Furthermore, we need to realize that even obese renal transplant recipients have a far greater survival benefit compared with other renal

replacement therapies such as dialysis. Data has shown that patients with a BMI of 40 and higher have a 48% reduction in the risk of death during five years of follow-up. If the BMI is lower than 40, this reduction is even higher (more than 66% within the aforementioned follow-up).[19]

In the third part of the thesis we discuss other extended criteria of potential live kidney donors. As we revealed with our survey amongst transplant professionals, next to an increased body weight, the presence of vascular multiplicity in donors is also considered as a potential contraindication to live kidney donation in some centers (between 7% and 9%). This is because having multiple renal arteries may lead to intraoperative technical difficulties and complications, such as increased operative time, complicated dissection, or bleeding. Furthermore, either (arterial) reconstructions need to be created after extraction of the kidney or multiple arterial anastomoses are needed in the recipient, both associated with an increased risk for (urological) complications.[20-22] Literature reports that a renal transplant recipient who receives a donor kidney with multiple arteries has a greater chance of associated complications of arterial stenosis, segmental infarction, hemorrhage, urine leakage, and ureteral stenosis.[22] Due to longer ischemia times, the incidence of acute tubular necrosis or delayed graft function could also be higher. The presence of more renal vessels often requires vascular reconstructions prior to implantation of the donor organ or multiple anastomoses can be made during implantation. Literature reports however that outcome between vascular reconstructions 'on the bench' and multiple anastomoses do not differ.[23,24] In the cohort analysis of live kidney donors that donated in the Erasmus MC between 2006 and 2013 (n=951), about 25% of the donated kidneys had more than one renal artery or vein. As expected, both warm ischemia times and skin-to-skin times were longer if vascular multiplicity was present. As only Clavien-Dindo Grade I complications (predominantly hematoma formation, urinary retention, and wound infection of the Pfannenstiel incision) were higher if venous multiplicity was present, we can safely conclude that vascular multiplicity has little potential negative impact on the donor. Regarding renal transplant recipients of a kidney with vascular multiplicity, the incidence of delayed graft function was seven percent higher in recipients receiving a donor kidney with more than one renal artery. However, hospital stay, graft- and patient survival were not compromised compared with kidneys with singular vascular anatomy. In conclusion, with modern surgical techniques and high surgical skills, neither renal artery multiplicity nor venous anomalies seem to pose any danger to the living kidney donor.

The presence of kidney stones in potential donors also leads to discussion. Again, guidelines make no hard statements, and based on the results of our survey, over 25% of transplant centers reject potential donors with one or more kidney stones. Therefore, a systematic review was performed, next to an analysis of our own cohort that donated a kidney (n=1555) between 1994 and 2014 and outcome of respective recipients. Current guidelines are fairly strict regarding the inclusion of a potential donor with one or more kidney stones. Data from literature suggests however, that these donors have comparable outcome and that only a few recipients of a stone-forming kidney develop stone-related complications that are all successfully treated. The prevalence of donors with kidney stones in our cohort was

2.3% (n=36), of which 21 kidneys with one or more stones were transplanted. In the other 15 cases, the kidney without stones was transplanted. In the recipients receiving a stone-bearing kidney, 14.3% (n=3) developed stone-related complications, which were all successfully treated. Based on both the literature and cohort analysis, we conclude that the presence of kidney stones should not be considered as an absolute contraindication to donation.

Since we now know that several comorbidities should not pose a problem for a successful and safe donation and transplantation, the aim would be to further expand the donor pool by including these extended criteria donors, while ensuring careful assessment of long-term follow-up.

FUTURE PERSPECTIVES

The question that rises after reading this thesis is how to implement the new insights regarding the extended criteria live kidney donors? What are the practical consequences for donor screening and informed consent regarding the potential live kidney donors in the future?

One of the most important issues that still have to be sorted out is what to do with potential live kidney donors with multiple extended criteria. We now know of several individual extended criteria that short-term outcome is good, but good outcome of donors with more than one extended criterion and their respective recipients still has to be confirmed. One of the possibilities would be to create a so-called 'donor risk index'; an algorithm in which several components can be imputed, providing a score on which both donor- as recipient risk can be predicted. Such a score already exists in the field of liver transplantation and for deceased donor kidneys, to calculate the outcome of a recipient given certain donor criteria, but obviously the new element in this donor risk index would be the addition of the risk for the live donor on the long-term.

In case of risk calculation in a potential donor, for example, if a transplant professional has two potential live kidney donors for one recipient; A 38 years old male potential donor with a BMI of 34, hypertension (controlled with one agent) could have a completely different risk profile compared with a female potential donor with a BMI of 31 and three renal arteries on both kidneys. In this case, a donor risk index could then assist in this choice. Naturally, in order to create such a model, it would require a large number of kidney donors. An (inter)national database for collecting data of (extended criteria) donors could contribute to this ideal.
However, before this can be achieved, we should closely watch the long-term outcome of extended criteria donors that have already donated their kidney. If the transplant community would be ascertained that these donors perform as well as 'standard' criteria live kidney donors, the next step would be to create such a donor risk index. Transplant professionals will then be able to define exact risks for a potential donor and the recipient, helping to decide whether he or she is suitable for donation, and

that optimal outcome of the recipient is ensured. Furthermore, in this way, a potential donor is optimally informed, providing a way to ease the final decision of donating a kidney.

RECOMMENDATIONS

With the new insights in this field, a proposal for guideline revisions regarding extended criteria live kidney donors could be as follows:

- Obesity
    - Donors with a BMI below 35 should be advised to lose weight before donation, but can be safely included if no additional technical surgical difficulties are to be expected.
    - Donors with a BMI above 35, combined with other comorbidities should lose weight, and if conventional methods fail, bariatric surgery may be advised.
    - Donors with a BMI above 40 should lose weight, and if conventional methods are unsuccessful, bariatric surgery should strongly be advised.
- Hypertension
    - Donors with hypertension that is well controlled with up to two antihypertensive drugs according to the current guidelines can be safely included.
- Older age
    - Potential donors older than 70 should be assessed on basis of biological age, rather than calendar age.
- Vascular multiplicity
    - Donors with vascular multiplicity should not be excluded. Although vascular multiplicity may present a challenge to the donor's surgeon, inherent longer operative times have no negative impact on outcome of the donor.
- Women of childbearing age
    - Women of childbearing age can be safely included as donors, but the increased incidence of preeclampsia should be part of the routine discussion about the risks of donation during the informed consent procedure.
- Minors as donors
    - Minors as donors (younger than 18 years) should not be considered for donation, although in some situations, the benefit of a recipient may outweigh this reluctance because of ethical considerations.
- Kidney stones
    - Donors with kidney stones should not be excluded on beforehand, as there is no evidence that these donors have impaired outcome. In case of the presence of bilateral stones, it should be noted that both donor and respective recipient have theoretical chance on developing stone-related complications.

- In case of a difficult renal transplant recipient (i.e. a recipient that is highly sensitized due to several previous transplantations), transplant professionals should be less reluctant to include an extended criteria live kidney donor.
- With the use of these guidelines, consensus should be reached on how to proceed in screening and selecting this specific group of donors.
- A uniform informed consent procedure for live kidney donors should be drafted and implemented, to ensure that every donor and recipient receives the same information regarding pre-, peri- and postoperative risks and complications.
- For extended criteria donors, a specific informed consent procedure should be drafted in which these donors are informed of the latest data (risks and complications) and knowledge.
- Ideally, a large international database should be set up to collect data of live donors to achieve more insight in (long-term) follow-up of standard as well as extended criteria donors.
- New surgical techniques are still being developed (robot-assisted donor nephrectomy, laparo-endoscopic single-site donor nephrectomy, natural orifice transluminal endoscopic surgery) to ensure donor comfort. However, transplant professionals must be aware that there is little room for improvement as the current techniques already show excellent results.
- The value of laparoscopic/robot-assisted kidney transplantation may be explored in obese renal transplant recipients to reduce (surgical) complications.
- The transplant community should institutionalize long-term follow-up of all donors to ensure donor safety, specifically in extended criteria donors.
- A donor risk index should be created, to be able to calculate peri- and postoperative risks, for both donors as well as their recipients.

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Chapter 12

Appendices

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Mijn copromotor, dr. FJMJF Dor. Beste Frank, eind 2009 kwam ik je voor het eerst tegen in OK 14, waar na vijf minuten bleek dat we allebei Erasmiaans alumni waren. Ik besloot hier gebruik van te maken en te vragen of ik wellicht m'n keuzeonderzoek bij de chirurgie kon regelen, na het voltooien van m'n coschappen. 'Stuur vanavond je CV maar even'. Ondanks het feit dat mijn 'CV' destijds nagenoeg inhoudsloos was, is er nu ruim vijf jaar later, dit boekje. Dank voor je eindeloze enthousiasme, de sms'jes om half twaalf 's avonds: 'nog wakker? ff bellen?', de diners 'ik vind alles best zolang het maar Aziatisch is', je regelmatige 'm'n Mac doet het niet, kan je ff kijken?' en je immer kritische -'wat ook nog wel in boekje kan'- blik. Je enthousiasme blijkt besmettelijk, want één ding is zeker; we zijn nog niet klaar!

De leescommissie, prof.dr. W. Weimar, prof.dr. H.W. Tilanus en prof.dr. T. van Gelder, dank voor het beoordelen van mijn proefschrift.

Speciale dank gaat uit naar de secretaresses van de afdeling Heelkunde. Carola, zonder jou was dit alles me vast ook wel gelukt, maar een stuk minder efficiënt dan het nu gegaan is! Dank voor het luisterend oor, het feilloos inplannen van afspraken waar deze onmogelijk leken en je hulp in de strijd tijdens de enerverende discussies met de personeelsadministratie om de declaraties er doorheen te krijgen. Conny, na mijn 'akte-fase' in 2009 zei je: 'het komt wel goed met jou, let maar op'. Het begint er zowaar op te lijken dat je gelijk krijgt! Bedankt voor je vertrouwen en support.

(Ex-)kamergenoten van Z-839; Niels 'ff harder, lekker nummertje', dank voor je regelmatige muzikale updates op het gebied van de laatste trance-hits. Inez, inmiddels bij de Urologie, zet 'm op! Bo 'gast, mag ik je broek lenen', ik hoop dat die meeting bij de professor goed gegaan is!! Coebergh, zie volgende pagina.

Collega's uit de Z-flat, dank voor al het plezier, jullie gewilligheid om al mee te gaan lunchen om 11:55, voor het feit dat er altijd wel eten voor me was, jullie extreme zorgzaamheid voor het Nespresso-apparaat, en dat er geen dag saai te noemen was.

James, wie had er beter m'n kaft kunnen ontwerpen dan jij! Het resultaat is schitterend, het blijft een feest om te zien hoe snel je dit doet en jezelf blijft verbeteren. Ik hoop dat we in de toekomst wellicht weer een nieuw project kunnen opstarten, jij het design, dan doe ik de rest wel!

Robby, ook jij hebt indirect bijgedragen aan het tot stand komen van dit boekje, woensdag 'patat-dag' is inmiddels een begrip bij m'n collega's. Beste patat van Rotterdam was een terechte prijs, na zestien jaar ben jij nog steeds m'n persoonlijke favoriet!

Vrienden van het Erasmiaans; Martijn, Olivier, Rochus en Stephan; Al meer dan vijftien jaar vallen we elkaar dagelijks lastig, hoop dat dit nog even door gaat. Martijn 'dr. Maus', jij bent de enige échte wetenschapper van ons, moge dat duidelijk zijn. Olivier, jouw carrière als eerste(?) bestuurskundige singer-songwriter is bijzonder, nu al je eerste EP-release achter de rug, alle respect hiervoor. Heel veel succes! Rochus, onze internist in spé, succes met je promotie bij de Metabole Ziekten! Stephan, ik hoop dat ik nog regelmatig onder het genot van een goede biefstuk van onze gesprekken mag genieten.

Paranimfen: Nikola 'broertje', menig keer zijn we met elkaar verward, zowel in de kroeg als in het ziekenhuis. Een alinea is niet genoeg om alle mooie verhalen samen te vatten, maar het moge duidelijk zijn dat jij een bijzondere plek inneemt. Jouw trouwe aanwezigheid in spannende tijden zal ik niet vergeten. Dat is iets waar de familie en ik je heel dankbaar voor zijn! Nu in opleiding tot cardioloog (het op-een-na-mooiste vak) in het Ikazia, heel veel succes, je bent een topper!

Coebergh, alhoewel we elkaar al min of meer kenden vanuit de college banken, begon de pret pas echt toen je in Z-839 arriveerde. Ik kan me geen dag herinneren waarop er niet gelachen is, jij uit het raam hing (laat je 'm voortaan heel?), of m'n stoel weer op standje 'begane grond' gezet hebt. Ik een duizendtal bijnamen rijker, jij wat chocoladerepen armer, en straks allebei kaal, wat willen we nog meer?

Alle anderen die een speciale plek hebben ingenomen de afgelopen jaren; Merel, Ellen, Jan-Willem, Peter en Guus. Bram, Sophie, Sigrid, Nina, Marjolein, Koen en Adinda. Dank voor jullie liefde, support en gezelligheid.

Ouders: cliché, maar waar; zonder jullie was ik nooit zo ver gekomen. Ook jullie bedankt voor de steun, het aanhoren van alle verhalen en de liefde door de jaren heen. Moeder, jouw aanwezigheid op mijn verdediging is al een feestje waard, dat je er nog bent dankzij de wetenschap waar ik de laatste jaren onderzoek in heb mogen doen, is op z'n zachtst gezegd bijzonder. Pap; alhoewel we niet vaak over de opstelling van Feyenoord of de laatste jurisprudentie hebben gesproken (mijn schuld), moge duidelijk zijn dat we wel degelijk op elkaar lijken, je onverstoorbaarheid, kennis, liefde voor echte muziek en werklust (vervelend hè, die verplichte vrije dag?) blijf ik bewonderen.

Last but not least, lieve Marijn, van alle mensen in dit dankwoord ken ik jou het kortst, maar zo voelt het niet. Dank voor het lachen, je luisterend oor, je verhalen, onze huiskamerconcerten, het me tot rust manen en zo af en toe het me weer met beide benen op de grond zetten. Jij hebt me weer laten zien dat niet alles zwart-wit is in het leven. Met jou naast me kan ik alles aan!

List of publications

LIST OF PUBLICATIONS

This Thesis:

Donors with stone-bearing kidneys are eligible for living kidney donation: a systematic review and cohort analysis
JA Lafranca, SF Durmaz, O Ivanovski, M van Bruggen, MGH Betjes, JNM IJzermans, FJMF Dor
Submitted

Complex vascular anatomy should not be a contra-indication for live kidney donation and transplantation
JA Lafranca, M van Bruggen, HJAN Kimenai, TC Tran, T Terkivatan, MGH Betjes, JNM IJzermans, FJMF Dor
Submitted

Perirenal and Intra-Abdominal Fat Mass Superior over BMI in Predicting Donor Outcome in Laparoscopic Donor Nephrectomy
JA Lafranca, LM Prens, M van Bruggen, A Moelker, M Koek, WJ Niessen, JNM IJzermans, FJMF Dor
Submitted

Attitudes among transplant professionals towards shifting paradigms in live kidney donation
JA Lafranca, EQW Spoon, J van de Wetering, JNM IJzermans, FJMF Dor
Submitted

Body Mass Index and outcome in renal transplant recipients: a systematic review and meta-analysis
JA Lafranca, JNM IJzermans, MGH Betjes, FJMF Dor
Accepted for publication: BMC Medicine

Shifting Paradigms in Eligibility Criteria for Live Kidney Donation: A Systematic Review
JA Lafranca, AR Ahmadi, LA Claessens, RMS Imamdi, JNM IJzermans, MGH Betjes, FJMF Dor
Kidney Int. 2015 Jan;87(1):31-45

The need for a standardized informed consent procedure in live donor nephrectomy: A systematic review
K Kortram, JA Lafranca, JNM IJzermans, FJMF Dor
Transplantation. 2014 Dec 15;98(11):1134-43

Systematic review and meta-analysis of the relation between Body Mass Index and short-term donor outcome of laparoscopic donor nephrectomy
JA Lafranca, SM Hagen, LFC Dols, LR Arends, W Weimar, JNM IJzermans, FJMF Dor
Kidney Int. 2013 May;83(5):931-9

Other publications:

Laparoscopic versus open peritoneal dialysis catheter insertion, the LOCI-trial; a single blind randomized clinical trial
JA Lafranca, SM Hagen, GP Akkersdijk, JJ Wever, HJAN Kimenai, M Wabbijn, AM van Alphen, JNM IJzermans, FJMF Dor
Submitted

Ischemic postconditioning in human DCD kidney transplantation is feasible and appears safe
EK van den Akker, DA Hesselink, OC Manintveld, JA Lafranca, RW de Bruin, W Weimar, JNM Ijzermans, FJMF Dor
Transpl Int. 2014 Feb;27(2):226-34

A systematic review and meta-analysis of the influence of peritoneal dialysis catheter type on complication rate and catheter survival.
SM Hagen, JA Lafranca, JNM IJzermans, FJMF Dor
Kidney Int. 2014 Apr;85(4):920-32

Laparoscopic versus open peritoneal dialysis catheter insertion: a meta-analysis
SM Hagen, JA Lafranca, EW Steyerberg, JNM IJzermans, FJMF Dor
PLoS One. 2013;8(2):e56351.

PhD Portfolio

PHD PORTFOLIO

Name PhD candidate: drs. Jeffrey A. Lafranca	PhD period: 2011-2015
Erasmus MC Department: Surgery	Promotor: Prof.dr. Jan N.M. IJzermans
Research School: Molecular Medicine	Supervisor: dr. Frank J.M.F. Dor

1. PhD training

General courses	**Year**	**Workload (ECTS)**
Basic Introduction Course on SPSS, Molecular Medicine Postgraduate School, Rotterdam	2013	1
Basiscursus Regelgeving en Organisatie (BROK), Erasmus MC, Rotterdam	2011	1.5
In-depth courses	**Year**	**Workload (ECTS)**
European Transplant Fellow Workshop (ETFW), European Society for Organ Transplantation, Prague	2014	0.5
OpenClinica Training, Erasmus MC, University Medical Center Rotterdam, Rotterdam	2014	0.1
European Society for Organ Transplantation- Introductory Program to Transplantation & Hesperis Course, Sophia Antipolis	2013	1
European Society for Organ Transplantation - Evidence in Transplantation Course, Royal College of Surgeons of England, London	2013	0.5
Winterschool, Dutch Kidney Foundation, Driebergen	2013	0.5
Repeated Measurements in Clinical Studies, Netherlands Institute for Health Sciences, Department of Biostatistics, Erasmus MC	2011	1.4
Biostatistics for Clinicians, Netherlands Institute for Health Sciences, Erasmus Winter Programme	2011	1.0
Introduction to Clinical Research, Netherlands Institute for Health Sciences, Erasmus Winter Programme	2011	0.9
Regression Analysis for Clinicians, Netherlands Institute for Health Sciences, Erasmus Winter Programme	2011	1.9
Courses for the Quantitative Researcher, Netherlands Institute for Health Sciences, Department of Biostatistics, Erasmus MC	2011	1.4
Oral presentations at (inter)national conferences	**Year**	**Workload (ECTS)**
European Society of Surgical Research, Annual Congress, Budapest	2014	3
European Organ Donation Congress, Budapest	2014	2
Live Donor Nephrectomy (LIDO) Course, Rotterdam	2014	1
PhD-Day Erasmus MC, University Medical Center Rotterdam	2014	1
Nefrologiedagen, Veldhoven	2014	1
Bootcongres, Leiden	2014	1
Eerste Rotterdamse Obesitas Symposium, Sint Franciscus Gasthuis, Rotterdam	2013	1
Congress of the European Society for Organ Transplantation, Vienna	2013	1
The 3rd Live Donor Nephrectomy (LIDO) Course, Rotterdam	2013	1
International Congress of the Transplantation Society, Berlin	2012	1
World Congress of Pain Clinicians, Granada	2012	1

Bootcongres, Dutch Transplantation Society, Maastricht	2012	2
Chirurgendagen, Veldhoven	2012	2
European Society of Surgical Research, Annual Congress, Lille	2012	2
Attended (inter)national conferences	**Year**	**Workload (ECTS)**
Bootcongres, British & Dutch Transplantation Societies, Bournemouth	2015	1
World Transplant Congress, San Francisco	2014	1
Symposium Experimental Research Surgical Specialties (SEOHS), Maastricht	2013	1
Klinisch Review Symposium, Dutch Transplantation Society, Utrecht	2013	1
Chirurgendagen, Nederlandse Vereniging voor Heelkunde, Veldhoven	2013	1
Ethical, Legal and Psychosocial Aspects of Transplantation (ELPAT) Congress, Rotterdam	2013	1
Bootcongres, Dutch Transplantation Society, Duiven	2013	1
American Transplant Congress, Boston	2012	1
Congress of the European Society for Organ Transplantation, Glasgow	2011	1
European Society for Surgical Research, Annual Congress, Aachen	2011	1

2. Teaching

Supervising practicals and excursions, Tutoring	**Year**	**Workload (ECTS)**
Examination of Basic Life Support (EHBO) of medical students	2011 -2014	1
Tutoring student Richa Spoon	2014-2015	1
Tutoring student Lisette Prens	2013-2014	1
Tutoring Minor- thesis Ali Ahmadi	2012	1
Tutor to first year medical students	2013	1
Tutor to first year medical students	2011	1
Lecturing medical students	2011-2014	4
Supervising Master's theses	**Year**	**Workload (ECTS)**
Tutoring Saïd Durmaz (Master- thesis)	2014-2015	2
Tutoring Mark van Bruggen (Master- thesis)	2014-2015	2

Curriculum Vitae

CURRICULUM VITAE

Jeffrey Anthony Lafranca, was born on October 8th 1987 in Rotterdam. After graduation from high school at the Erasmiaans Gymnasium in Rotterdam in 2005, he started his medical studies in Rotterdam as well at the Erasmus University Rotterdam. He obtained his medical degree in 2011. From 2011 to 2012, he worked as a surgical resident in the Erasmus MC, University Medical Center Rotterdam. In 2012, he started as a PhD-candidate, in the field of transplantation surgery under supervision of dr. Frank Dor and Prof.dr. Jan IJzermans, which has resulted in this thesis.